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THE BRITISH JOURNAL OF TUBERCULOSIS AND DISEASES OF THE CHEST

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BRITISH JOURNAL OF TUBERCULOSIS
AND DISEASES OF THE CHEST

Vol. L. JULY, 1956 No. 3.

THE VALUE OF BRONCHOGRAPHY IN DIAGNOSING "PERIPHERAL" PRIMARY LUNG CARCINOMA

BY CLAYTON L. N. ROBINSON
AND
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THE recorded deaths from carcinoma of the lung have shown a progressive annual increase. That this is due to more than an increased awareness of the disease and better methods of diagnosis has been proved (Stocks) by the standardised death rate in males, which rose from 1·1 in 1920 to 10·6 in 1938.

Surgery is still the sheet anchor of curative treatment. The collected results of Taylor and Waterhouse had a five-year survival rate of 13 per cent. in 313 pneumonectomies. More recently, in a personal series of 273 resections (1940-48), Holmes Sellors had a 21 per cent. five-year survival rate—or, of those surviving the post-operative period, 27·5 per cent.—and the prognosis for the years 1949-50 was considerably better. Bignall and Moon analysed the results obtained at the Brompton and London Chest Hospitals: the gross survival rate after five years in 453 patients with resections who left hospital (operative mortality 14·7 per cent.) was 33 per cent. While these results are excellent, a large percentage of cases are already beyond curative treatment when first diagnosed. Few of the ancillary aids for confirmation of bronchial epithelial tumours are of practical use for early lesions.

Cytological examination of the sputum for malignant cells is valuable, but is a specialised technique and requires a careful search by an experienced pathologist. Bronchoscopic biopsy is a satisfactory method of confirmation for proximal growths; but in many cases where it is positive, the condition is hopelessly advanced. A study of our statistics strengthened this view.

DETAILS OF FINDINGS IN THIS SERIES

The last 250 cases have been analysed in relation to the rôle of bronchoscopy in diagnosis and the subsequent surgical procedure. The bronchoscopic evidence has been considered positive either when a biopsy was proved histologically, or when the biopsy was negative (that is, the correct portion of the tumour was not secured), but the diagnosis was proved later. The bronchoscopic evidence was classified as inconclusive or negative when a completely normal bronchial tree was observed, or some evidence such as localised inflammation, smooth stenosis, intersegmental carinal widening or external pressure was seen.

(*Received for publication December* 31, 1955.)

	Total	*Bronchoscopy positive*	*Bronchoscopy negative*
Inoperable thoracotomy or other reasons ..	94	59 (63%)	35 (37%)
Pneumonectomy	111	60 (54%)	51 (46%)
Lobectomy	45	8 (18%)	37 (82%)

It is clear that a negative bronchoscopy does not exclude a neoplasm, and other methods must be found to facilitate a diagnosis in the early lesions. What value has bronchography in diagnosing this lethal condition?

Bronchograms have been done recently in every case in which the bronchoscopic evidence was negative, to analyse the features of neoplastic bronchial obstruction. It is safe to say that, excluding Pancoast tumours and the rare alveolar cell lesion, they have been diagnostic in over 90 per cent. of tumours. We have found that in the presence of peripheral carcinomata (tumours beyond bronchoscopic vision have been called "peripheral") the appearances have taken the form of:

(1) An abrupt arrest—transverse or oblique; smooth or irregular; concave or convex. (Figs. 1-4; Fig. 7.)
(2) A rat-tail irregular defect. (Fig. 5.)
(3) Lateral irregular defect. (Fig. 6.)
(4) A missing branch. (Fig. 8.)

(1) and (2) should be differentiated from a longer smooth obstruction, as seen, for example, in the middle lobe syndrome, possibly with a calcified lymph node lying extrinsically.

It is important to note that these defects are only of significance when the other segmental bronchi are well filled to the periphery and the affected one is in the region of the segmental shadow seen on the plain film. It is also essential that the clinician doing the bronchogram should be responsible for obtaining satisfactory filling of the tree.

It is sometimes argued that bronchograms are useless in the diagnosis of neoplasms because retained secretions show false blocks as well. It is true that secretions cause difficulties in interpretation, but with a primary neoplasm they do not, as a rule, cause trouble (Fig. 6), whereas with a suppurative pneumonitis of a lobe, or an abscess in a segment, several segmental bronchi will show apparent blocks, and this serves as a distinguishing feature.

Another practical use for the demonstration of bronchial blocks is the case of the elderly man with a peripheral shadow; if he is unfit for thoracotomy but deep X-ray therapy is needed, then demonstration of a typical bronchial block is definitive. In such a case, there need be no danger of irradiating a doubtful and possibly inflammatory lesion. (Fig. 4.)

We have also found the bronchogram helpful in excluding intrabronchial obstruction. In the differential diagnosis of an unresolved or slowly resolving pneumonia, when bronchoscopy has been "negative," a bronchogram is useful in showing the blocked bronchus due to neoplasm (Fig. 7), whereas an orthodox resolving pneumonia may have bronchi filled satisfactorily to their termination.

The bronchogram is useful in excluding or confirming neoplasm where more than one system is involved. This is particularly so when the other site is cranial.

FIG. 1.—J. H.: Male æt. 47.—Pain left chest for 3 days. Smoker's cough (10 days). W. B. C. 5,800. Bronchoscopy: N.A.D. Bronchogram and bronchotome: transverse block in branch of posterior segment L.U.L.; Lt. U. Lobectomy-oat cell lesion.

FIG. 2.—O.W., Male æt 54.—P.T.B. 2 years previously treated with P.A.S. and Streptomycin; P.P. for 12/12. Then shadow developed Rt. base, not affected by drugs. W.B.C. 9,500; E.S.R. 2 mm. Bronchoscopy negative. Bronchogram: Right posterior basic showed oblique defect. Rt. L. Lobectomy: squamous lesion.

FIG. 3.—C.W.: Male, æt. 54—Cough and sputum; pain in Rt. chest 3/12. One course of penicillin and chloromycetin without clearing; 1st degree clubbing. W.B.C. 12,200; E.S.R. 38. Bronchoscopy: N.A.D. Bronchogram: convex block M.L. Thoractomy = Pleural metastases and mass in middle lobe.

FIG. 4.—F.L.: Male, æt. 69.—Recurrent bronchitis. Recent exacerbation of cough and staining. Loss of 3-4 stone. Clubbing of fingers; cyanosis. W.B.C. 18,000; Hb. 69 %. E.S.R. 50. Bronchoscopy: N.A.D. Bronchogram: Concave block posterior segment R.U.L. Unsuitable for thoracotomy. Treated D.X.R. with clearing.

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FIG. 5.—W.F.: Male, æt. 46.—'flu for 3 days. Cough and staining. Early clubbing. Bronchoscopy: N.A.D. Bronchogram: rat-tail defect anterior segment R.U.L. Pneumonectomy: oat cell lesion. Subcarinal nodes involved.

FIG. 6.—A.B.: Male, æt. 41.—Recurrent pain Lt. chest; excessive sweating; 6 months' multiple joint pains. X-ray: flare Lt. upper lobe. Bronchoscopy: Pus coming from apicoposterior segment. Bronchogram: Distortion of upper lobe bronchi and lateral defect in apicoposterior segment. Left Pneumonectomy: hilar nodes not invaded. Squamous lesion.

FIG. 7.—V.T. Male, æt. 48.—3 weeks' productive cough and staining on two occasions; excessive sweating; pain in Lt. chest; loss of appetite. W.B.C. 12,400. Heavy smoker. X-ray showed consolidation in Lt. upper lobe; treated with Estopen for 2 weeks without resolution. Bronchoscopy showed slight concentric narrowing of L.U.L. bronchus; the "blind" biopsy was of chronic inflammatory tissue. Bronchogram: obstruction of apicoposterior and anterior bronchi with lingula pulled upwards. Left Pneumonectomy. Hilar lymph nodes not invaded. Squamous lesion.

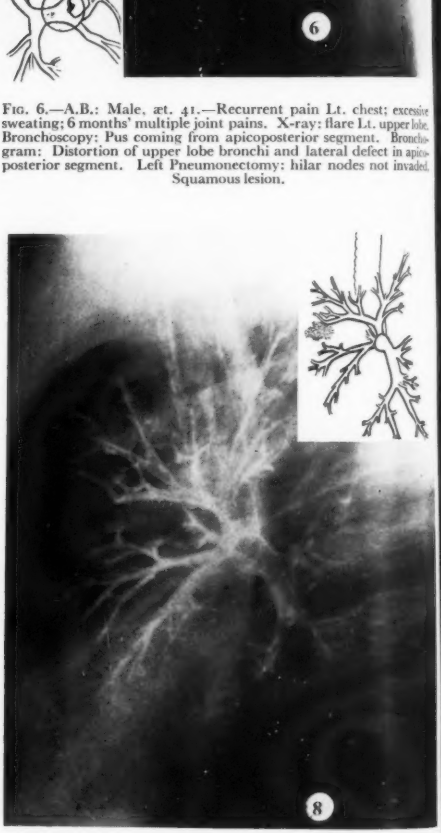

FIG. 8.—G.B.S., æt. 55, male.—Chronic bronchitic. 4 mos. before febrile illness with rigor, clearing in 3 wks. with antibiotics. 2 mos. before, X-ray showed shadow L.U.L. Concomitant dysuria, nocturia and hæmaturia investigated—no serious lesion found in urinary tract. Bronchoscopy N.A.D.; secretions from L.U.L. negative for neoplastic cells; Bronchography showed fifth division branch in anterior segment "missing", in region of peripheral shadow. Radical resection of L.U.L. Histology: poorly differentiated squamous neoplasm without involvement of hilar nodes.

We have found the bronchogram essential also in excluding primary neoplasms in cases presenting with hæmoptysis. When this is thought to be due, for example, to bronchitis or hypertension, an effective filling of all bronchi with contrast media in people with a "negative" bronchoscopy is a supplemental requisite before a firm diagnosis may be made. It is easy to recall cases dismissed with "bronchitis" who returned six months later with obvious neoplasms.

Discussion

With peripheral lung lesions, the bronchogram has been as important a diagnostic aid in confirming or excluding a neoplasm as barium enema would be for colonic lesions beyond the reach of the sigmoidoscope.

With the advent of Dionosil, there need be no fear of residues of contrast media confusing later pictures. As Dionosil is expectorated or otherwise eliminated satisfactorily in a few days, it is not necessary to wait as long as previously before operation.

We now feel that bronchography has supplanted tomography as a means of locating bronchial obstruction (and subjects the patient to fewer X-rays), rather than the reverse. Tomography will differentiate a breaking down solid lesion and certain techniques may demonstrate bronchial obstruction; but for the majority of peripheral lesions it may show a spurious block when a bronchus is not parallel to the casette. Other procedures are useful for advanced lesions: angiocardiography, an examination not in general use, is finding a place in differentiating inoperable from operable growths (Slesser); scalene node biopsy (Daniels) is a helpful method for confirming a diagnosis in lower as well as upper lobe lesions, but when it is positive the case is advanced; a barium swallow showing deformity of the œsophagus in the presence of a bronchial neoplasm usually points to irresectability (Middlemass). Furthermore, Vim-Silverman needle biopsy of lung (Dutra and Geraci) is dangerous, and paracarinal biopsy is of no value with peripheral lesions (Radin).

Although a high proportion of symptomless, intrathoracic opacities are malignant—Cruickshank (1952) has a 15 per cent. incidence in fifty-two cases—it is a mistake to make a standing rule that all solid pulmonary lesions warrant radical treatment. Liavaag reported six cases in which he had probably done pneumonectomy needlessly (two for pulmonary tuberculosis, two for chronic pneumonitis, one for innocent bronchial stenosis and one for bronchiectasis). An operation may be avoided or healthy lung tissue may be conserved if an exact diagnosis can be made by radiological exploration of the bronchus before operation is advised. In addition, the doubts of the surgeon may be lessened during a partial or total lung resection if he is sure of the pathology he is removing. It might be argued that during thoracotomy with a doubtful lesion, a local excision should be done first and frozen section performed. This is time-consuming, and the lession which is confounding macroscopically is often difficult microscopically also.

A criticism of trying to demonstrate a bronchial origin for peripheral tumours was the feeling that while central or hilar tumours arise in the bronchus—and the majority were thought to arise in main or lobar bronchi—peripheral tumours do not. This assumption developed from necropsy studies on advanced

lesions. However, Walter and Pryce in 207 surgically resected specimens were able to locate definitely the site of origin of growth in 59·4 per cent., while in a further 18·4 per cent. the probable site was found. Tumours were classified according to a site of origin into three groups: central, arising in one of the nominate bronchi; intermediate, arising in a macroscopically visible branch of one of the nominate bronchi; and peripheral, arising in one of the minute bronchi or bronchioles. Of the definitely located tumours, 47·1 per cent. were central, 3·3 per cent. intermediate, and 49·6 per cent. peripheral. They found bronchial obstruction to be a distinctive and constant feature of central tumours. When peripheral tumours showed naked-eye bronchial involvement, it was due to invasion either from the primary growth directly or from secondary lymph nodes.

If tumours out of reach of bronchoscopic vision were called peripheral, this group would constitute a great number of those resected. In this respect, a tumour which appears to be a central one in a postero-anterior radiograph is often seen to be peripheral on the lateral film; for example in the apical segment of the lower lobe.

The problem of diagnosing peripheral lesions early is of some importance. The prognosis is better and the operative mortality less for lobectomy when this is done as a " curative " procedure. Aufses had a 26 per cent. five-year cure rate in 53 lobectomies, as compared to 17 per cent. of 112 pneumonectomies. He calculated that without node involvement the cure rate was 30 per cent., and 6 per cent. with it. R. H. Overholt has surveyed the " silent " lesions prior to 1950: six out of eight, or 75 per cent., of those treated within three months of the first X-ray were still alive, and only five of twenty-two, or 23 per cent., of those treated after three months of the first X-ray were still living. Ochsner had better results with peripheral than central lesions: of 195 cases, the fatality rates with regard to site as to main, lobar, and peripheral portions of the lung were 79, 71 and 68 per cent., respectively.

It is evident that peripheral lesions, although tending to spread by the blood stream, are usually most favourable for surgical treatment, and are often watched beyond the time when a cure is possible. In fact, the average delay before operation in lung cancer of six to eight months is often condemned, but then it is reasoned that if the diagnosis of a peripheral lesion is obscure, serial skiagrams should be taken to see whether or not it increases in size. With peripheral discreet shadows, bronchography should be used to supplement bronchoscopy and the physician immediately concerned with management of a case should try to narrow the diagnosis possibilities without further delay.

Summary and Conclusion

(1) The rôle of bronchoscopy and biopsy in 250 cases has been assessed. Bronchoscopy was " negative " in 37 per cent., 46 per cent., and 82 per cent., respectively, of patients who were inoperable, had pneumonectomy and lobectomy.

(2) Bronchography has been done on all cases having lesions beyond bronchoscopic vision and has been diagnostic in over 90 per cent. of tumours. The radiological features of obstruction have been: abrupt arrests—whether trans-

verse or oblique, smooth or irregular, concave or convex; rat-tail irregular defects, lateral irregular defects and a missing branch.

(3) Bronchography should be done routinely to supplement bronchoscopy when a peripheral shadow is first seen, in preference to waiting to see if it increases in size.

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MASSIVE COLLAPSE OF THE LUNG WITH ACUTE RESPIRATORY INFECTION

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In the years following the 1914-18 war there was considerable interest in massive collapse of the lung. Jackson and Lee (1925) reviewed the subject and concluded it was mainly a post-operative event. Coryllos and Birnbaum (1928) associated its onset with plugging of a bronchus by tenacious mucous secretion, noting that any factor diminishing respiratory movement and coughing predisposed to its occurrence. Since then the main interest in massive collapse has centred on its prevention in anæsthetic and surgical practice.

Our attention has been drawn to the association of massive collapse with acute respiratory symptoms in five patients seen during the winter 1954-55. These presented with acute respiratory symptoms, sometimes associated with a tight sensation in the chest. Physical examination revealed a diminished respiratory movement, dullness on percussion and poor air entry over the affected area, with few or no adventitiæ. The chest radiograph showed an opacity confined by lobar boundaries, but the lateral view was usually most instructive, showing displacement of the pulmonary fissures towards the opaque lobe with some "bowing," indicating some degree of atelectasis (Figs. 1 and 2). The response to chemotherapy and physiotherapy was poor. Bronchoscopy, especially in later cases in which it was used at an earlier date, produced a quick response.

Case 1. P.M. Aged 56. Male. Married fitter. Past history of recurrent bronchitis with several episodes of "pneumonia" which responded to penicillin.

Admitted on 26.12.54 with an acute illness that had begun two weeks earlier, with general malaise, pyrexia, cough and sputum. Pain of pleural character later appeared in the lower right chest. Sputum, at first whitish, became thicker and yellow. He was pyrexial (T. 103° F.) with a slight cyanosis. Right chest moved little and there was poor air entry. Dullness to percussion was present at the right base and rhonchi were heard generally. X-ray showed consolidation in the right lower zone with some atelectasis. There was a leucocytosis of 16,000/cu. mm. (86% polymorphs). Sputum examination revealed only mixed respiratory flora. Penicillin and sulphasomidine (Elkosil) were given for five days. He remained pyrexial and the physical signs persisted. Aureomycin was used for eight days with little clinical or radiological change, but the pyrexia gradually settled. Atelectasis persisted in the right lower lobe. On 27.1.55 bronchoscopy revealed only some inflammation of the mucous membrane in the bronchi of both lungs. Aspiration was not done. Postural percussion and breathing exercises were then instituted. By 16.2.55 the clinical

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signs were lessening, but the X-ray remained unchanged until on 22.2.55 a film showed increasing aeration of the lower lobe. He was discharged to convalescence on 5.3.55.

Case 2. B.W. Aged 29. Housewife. In late October 1954 an illness began with coryza, and respiratory symptoms developed with a temperature of 105° F. Cough was present with little sputum, and dyspnœa was noticeable. Penicillin produced no effect. Admitted on 6.11.54 when the temperature was 102° F. She appeared alert. There was diminished movement of the chest at both bases where the percussion note was impaired and air entry diminshed. Crepitations were present at the right base.

White blood cells were 10,400/cu. mm. (68% polymorphs). Sputum contained mixed respiratory flora. Chest X-ray showed consolidation and atelectasis of the posterior segments of the right lower lobe. Aureomycin for five days produced no change. Bronchoscopy on 11.11.54 revealed "some inflammation of the basal bronchi, particularly the right posterobasal segment, with thick purulent discharge which was sucked out. No other abnormality seen." Next day the air entry had increased at the right base and clinical improvement was uninterrupted. On 22.11.54 an X-ray showed only a few linear shadows at the right base. She was discharged on 28.11.54. A final X-ray on 6.1.55 was clear.

Case 3. G.B. Male. Aged 28. Machine tool fitter. Past history of right pneumonia, 1948. On 22.12.54 he felt shivery and not quite well. He was sent home from work with headache, discomfort in the right chest and pain on deep inspiration. The temperature was 103° F. Vomiting occurred mid-morning and again in the evening. On 24.12.54 a productive cough appeared and he was admitted to hospital. He appeared flushed. Temperature 101° F., P. 94, R. 26. The right side of the chest moved little. There was dullness to percussion at the right base where breath sounds were distant. White blood cells numbered 10,200/cu. mm. (88% polymorphs). He was treated with penicillin, but the pyrexia continued.

X-ray on 28.12.54 showed a dense opacity in the right lower lobe with some atelectasis. Another on 3.1.55 showed the right middle lobe also to be opaque.

Postural percussion and expectorants were employed with little effect. The pyrexia slowly settled and by 10.1.55 the clinical signs of consolidation in the right lower lobe were still present but a little less marked. Chest X-ray showed a little clearing of the lung shadows.

Bronchoscopy on 13.1.55 showed considerable narrowing in the region of the right segmental bronchi. This appeared to be mainly due to inflamed or œdematous mucous membrane which bled easily when touched. Biopsy was taken and the histological findings were "Partial ulceration, the submucosa is congested and infiltrated with polymorphs, lymphocytes and histiocytes. There are some areas of distortion where the cells are not identifiable. The picture is that of an acute inflammation."

Next day air entry had improved considerably and an X-ray on 17.1.55 showed only scanty basal shadows, while on 24.1.55 it appeared clear. He was discharged on 28.1.55.

Case 4. T.J. Aged 17. Schoolgirl. About 15.12.54 she developed a febrile illness with pharyngitis and was treated with sulphathiazole. By 19.12.54 there was also a cough and a "noisy chest." Penicillin therapy was begun that day and sulphonamides ceased. On 23.12.54 she was seen by one of us for the first

time. She was febrile and there were signs of consolidation in the lower right chest. X-ray showed atelectasis of the apical and posterior segments of the right lower lobe. Penicillin was continued and she was encouraged to cough, the mother being instructed in postural percussion. The pyrexia settled and she brought up a little whitish sputum, but signs of consolidation persisted and an X-ray on 28.12.54 showed only slightly less extensive shadows. In view of this bronchoscopy was done on 6.1.55. While inserting the bronchoscope a plug of mucus was coughed up. The orifice of the middle lobe was reddened and flattened. Suction produced no further mucus. The clinical signs then disappeared and X-ray on 10.1.55 showed scanty residual shadows over the apex of the right lower lobe and she was discharged home. X-ray on 15.2.55 clear.

Case 5. S.B. Female. Aged 22. Single. Past history: Asthma in earlier life. On 1.2.55 a cough began but there was little upset until on 6.2.55 she awoke with a tight sensation over the lower sternum and this slowly became painful, involving the right and left shoulders, and by 8.2.55 there was continuous pain over the lower chest, worse on deep breathing. On admission to hospital she appeared flushed. Temperature was 99·6° F., P. 92, R. 20. Trachea and mediastinum were displaced to the left. The left side of the chest moved little and air entry was poor. An X-ray on the following day showed an opaque left lung and white blood cells were 22,200/cu. mm. (84% polymorphs). Sputum grew mixed respiratory flora. Penicillin and sulphasomidine were started and the next day bronchoscopy showed the left main bronchus to be completely blocked by thick purulent material which was aspirated.

On the following day she appeared better, trachea was central, movement of the left chest had increased, and a chest X-ray showed only partial atelectasis of the posterior basal segments of the left lower lobe. Improvement continued and an X-ray on 17.2.55 was clear (Figs. 1, 2, 3). She was discharged on 19.2.55.

Discussion

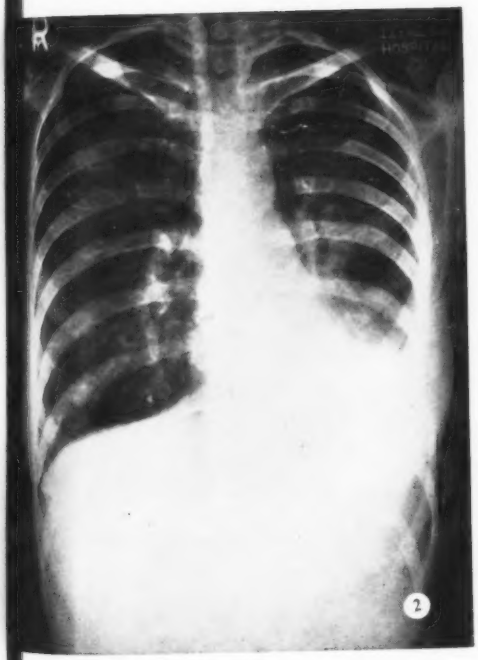
In patients of 40 or over unresolved pneumonia is always suspect as being possibly due to an underlying neoplastic obstruction. In lobar pneumonia massive collapse is not expected frequently since the affected portion of lung is usually solid. Reiman (1938) pointed out that "Minor degrees of atelectasis probably occur at various stages in most cases of pneumonia and are probably for the most part of no importance. In the occasional case, however, massive atelectasis may serve to explain the puzzling suppression of breath sounds and the misinterpreted signs of thickened pleura or pleural effusion which occasionally confront the examiner."

A review of the literature has revealed some cases similar to our series. Tidy and Phillips (1914) described a case with slowly resolving clinical signs of atelectasis in a young man. X-ray six weeks after the onset was normal. Mainzer (1931) described two cases. The first a man of 30, was considered to have lobar pneumonia but was becoming weaker and more dyspnœic. Chest X-ray showed an opaque right chest and bronchoscopy revealed obstruction of the right main bronchus with gelatinous material, some of which was removed by suction with dramatic improvement. The second case was a man of 43 with acute respiratory symptoms and a radiological opacity at the left base. Bronchoscopy revealed obstruction in the left main bronchus.

FIG. 1.—*Case V.* I. On admission—massive atelectasis L. Lung.

FIG. 2.—*Case V.* II. 11.2.55. The day after Bronchoscopy—considerable re-aeration of L. Lung.

FIG. 3.—*Case V.* III. 17.2.55. Clear.



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Aspiration failed but a sponge passed down the bronchoscope and twisted on itself withdrew gelatinous material. Recovery was then rapid. Miller (1950) described a woman with pyrexia and cough who had consolidation at the right base. Treatment with penicillin made her apyrexial but the right lower lobe remained opaque radiologically. At bronchoscopy a month later a tenacious, gelatinous plug was removed on the sucker with subjective improvement. The physical and radiological signs settled during the succeeding five weeks.

In younger people it appears that physical signs of unresolved pneumonia arise from bronchial obstruction due to tenacious, gelatinous exudation. There seems little benefit to be gained by continuing courses of chemotherapy in such patients, and we advocate the more frequent use of bronchoscopy in these people, not only for diagnostic purposes but also on therapeutic grounds. Such procedure should include the passage of a sucker down the affected bronchi even if the visible bronchi appear patent. In this series the course of the diseases has been considerably shortened by this procedure. Physiotherapy appears to be ineffectual and may well be responsible for sucking of the obstructing plugs further down the affected bronchi after expulsion of the air by percussion.

Summary

Five cases of pulmonary aelectasis occurring in acute respiratory infection s are reported. Chemotherapy and physiotherapy produced little improvement and the more frequent use of bronchoscopy is advocated in this type of case.

We wish to thank Dr. G. H. Jennings for permission to report cases I and V, Mr. R. Laird and Mr. T. W. Stephens for bronchoscopies, the several General Practitioners who referred these patients, and Dr. H. J. Trenchard for criticisms.

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SPONTANEOUS HÆMOPNEUMOTHORAX

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Spontaneous pneumothorax is sometimes complicated by bleeding into the pleural cavity. Although this clinical condition was known to physicians in the last century the first comprehensive reports are those of Rolleston (1900) and Pitt (1900). Since then about 150 cases have been reported (Calvert and Smith, 1955), mainly from America, the largest series being that of Hyde and Hyde (1951) with 12 cases. So far as can be ascertained only 24 cases have been reported in the English literature (Rolleston, 1900; Pitt, 1900; Ness and Allan, 1910; Bushby, 1913; Housden and Piggot, 1931; Tait and Wakely, 1935; Birch, 1936; Maxwell, 1938; Perry, 1938; Davidson and Simpson, 1940; McMyn, 1947; Borrie, 1953; McGown, 1954; Calvert and Smith, 1955; Clyne and Hutter, 1955; Agnew, 1955). Some cases from this country have been reported in American journals, including a series of six cases by Ross (1952).

Almeyda (1943) reported a case of spontaneous hæmothorax, a condition which may be considered to be clinically and pathologically similar to spontaneous hæmopneumothorax, although radiologically the presence of a pneumothorax cannot be demonstrated. Cases of spontaneous hæmothorax have been reported by Perry (1938) and Crawford and Shafar (1946).

The objects of this paper are to present eight cases of this condition, to refute its rarity and draw attention to special points in the diagnosis and management. There has been no attempt to survey the whole subject which has been well reviewed by Hopkins (1937), Hartzell (1942), Eidinger and Rubin (1952), and more recently by a comprehensive review of the literature by Calvert and Smith (1955).

Case Reports

These are summarised in the accompanying table, but the following case is reported in detail because of the importance of recognising that treatment with streptokinase and streptodornase may precipitate further bleeding.

Case 6. A machinist aged 18 years was well until three days before admission. He then felt cold and faint and began to sweat. This passed off. On the day before admission he developed pleuritic pain in the right side of the chest associated with breathlessness. He was referred by his general practitioner for a mass miniature radiograph of the chest which showed no abnormality. The following day he was admitted to hospital. He gave no previous or contact history of tuberculosis.

On admission on June 29, 1954, his general condition was good and he was not shocked. The temperature was 99·4° F. There were signs of fluid extending to the inferior border of the right scapula posteriorly. X-ray of the chest showed a hydropneumothorax and aspiration revealed the fluid to be blood. 150 ml. were removed. The hæmoglobin was 82 per cent. (Sahli).

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On the following day at 11.30 a.m., 900 ml. of blood were removed and no more could be aspirated. Five ml. streptokinase streptodornase mixture in normal saline (streptokinase 20,000 Christensen units; streptodornase 5,000 units) were instilled into the pleural cavity. Two and three-quarter hours later the patient suddenly became very breathless. The respiratory rate rose to 50 per minute, the extremities became cold and the pulse rapid and feeble. Movement of the right side of the chest was almost absent and the right side of the chest appeared larger than the left. The upper part was hyperresonant and the signs of fluid extended up to the fifth thoracic vertebra.

The patient was given oxygen and morphia. A needle was inserted into the right pleural cavity and the intrapleural pressure was plus 60 cm. water. The pressure was reduced to normal and 900 ml. of blood were aspirated. Cross-matched blood of the patient's group was transfused and after 100 ml. had been given the patient had a rigor and the transfusion was stopped. Transfusion was restarted with a different bottle of blood and a total of 4 pints was given without further trouble. The following day the patient was much improved and no further bleeding appeared to have occurred. The hæmoglobin was 90 per cent. (Sahli). Further aspirations were carried out, only small quantities up to 120 ml. being removed on each occasion. Serial X-rays showed diminishing fluid and increasing expansion of the lung. He was discharged from hospital after one month.

Two months after the onset radiological examination showed slight elevation of the right diaphragm with diminished movement and slight residual thickening down the right axillary margin. One year later he is well and X-ray of the chest shows only a few small pleural "peaks" on the right diaphragm.

(Tabulated Case Reports appear on pages 218-219.)

Comment

This patient is the only one of the series who was treated with fibrinolytic enzymes. Two and three-quarter hours after the injection of streptokinase-streptodornase he had an episode of extreme breathlessness, associated with severe shock and collapse, and required blood transfusion. There was evidence of bleeding into the pleural cavity and the intrapleural pressure was plus 60 cm. water. These findings could be explained on the basis that the patient had had a second pneumothorax associated with further tearing of adhesions. If this was the mechanism, streptokinase-streptodornase may have been instrumental in dissolving fibrin which had been plugging a ruptured subpleural bulla. On the other hand, streptokinase-streptodornase may have started bleeding from the original site of hæmorrhage.

A third possibility is that the state of shock was, in itself, a reaction to the enzymes and the blood-like fluid may have been the product of dissolving clots, but this does not explain the raised intrapleural pressure. Allergic reactions do occur with these substances. The patient had a rigor six hours after the injection of streptokinase-streptodornase and, at the time, this was thought to be a reaction to transfused blood. However, subsequent investigation showed the blood to be completely compatible and antibody tests were entirely negative. This febrile reaction was, almost certainly, the result of streptokinase-streptodornase therapy.

Discussion

Spontaneous hæmopneumothorax is thought to be an uncommon condition. In the seven years 1948 to 1954, 68 cases of spontaneous pneumothorax were admitted to the Royal Victoria Infirmary, Newcastle upon Tyne. Sixty-one of the cases were males and six were females. Eight cases, all males, were complicated by bleeding into the pleural cavity and these are reported above. This would agree with Chapman's (1950) claim that free intrapleural hæmorrhage occurs in about one in eight patients with spontaneous pneumothorax, although Hyde and Hyde (1951) in a series of 112 consecutive cases of spontaneous pneumothorax found five with blood in the pleural cavity, and Rottenburg and Golden (1946) reported three patients with spontaneous hæmopneumothorax in a series of 97 cases of spontaneous pneumothorax. Briggs *et al.* (1953) reviewed 84 cases of spontaneous pneumothorax and found only 3 cases of hæmopneumothorax.

This condition usually occurs in men between the ages of 15 and 45 who have previously been in good health. It has been said (Hyde and Hyde, 1951) that the patients are usually underweight, but this has not been confirmed in this series. Pain of sudden onset, which is sharp and stabbing, occurring on the affected side, is a prominent feature. It may radiate to the shoulder or abdomen and, in the latter case, if nausea, vomiting, abdominal rigidity and shock are present, an abdominal emergency may be simulated. Dyspnœa is usually present and may occur in the absence of pain (Case 2). The signs of a hydropneumothorax usually appear, and later shock and collapse, if the bleeding is rapid and marked. If the bleeding is slow the systemic signs of hæmorrhage may never appear.

In typical cases, with a short history and the signs of hydropneumothorax associated with shock and anæmia, the diagnosis is not difficult. Nevertheless, just as it is sometimes difficult to diagnose uncomplicated spontaneous pneumothorax on history and physical findings alone (Perry, 1939), in hydropneumothorax diagnosis can only be conclusively established by radiological examination. It may be necessary to take films with the patient lying on his sound side (Yater and Rodis, 1933). Case 2 and Case 6 presented only with the signs of a pleural effusion. The nature of the fluid should always be determined by diagnostic aspiration, otherwise hæmothorax may not be discovered and subsequent organisation leads to the development of fibrothorax. Aspiration was delayed for seventeen days in Case 5, as it was considered that the patient had a simple effusion associated with spontaneous pneumothorax. The presence of a variable amount of fluid is not uncommon in spontaneous pneumothorax. Fluid was found in 18 cases of the series of 68, these cases being additional to the eight cases of hæmopneumothorax. Fluid was most commonly present radiologically about the end of the first week.

Each case requires individual assessment with a view to treatment. Emergency thoracotomy, after resuscitation, has recently been recommended for all cases (Clyne and Hutter, 1955). Although a less conservative policy with regard to operation is now accepted, there are some cases which are so mild, or whose course, under non-operative treatment, gives no cause for anxiety, that thoracotomy is not justified. Nevertheless it is felt that all cases should be

in a hospital where thoracotomy could be carried out if this becomes necessary as an urgent measure.

It must be emphasised that general measures, such as transfusion, oxygen and sedation, should be adequate to control the shock in all cases. Deterioration may otherwise occur and the patient be unfit for operation. In milder cases transfusion may not be required, but all cases should nevertheless have the blood group determined. Systemic antibiotics may be given, but intrapleural penicillin, in some cases, appears to have an irritant effect and causes a higher fibrinogen content in the pleural fluid than usual (Sellors, 1945).

Careful aspiration of air and blood is required; bleeding tends to cease with the lung expanded. Repeated aspiration may not be easy with an ill patient and it is probably better to use an intercostal catheter attached to a water seal. It may be necessary to introduce another catheter anteriorly, into the second interspace, to allow air to escape more easily. Aspiration with air replacement may hinder recovery and is not now advised (Sellors, 1951).

If bleeding continues thoracotomy should be carried out. In addition to control of bleeding this allows removal of blood clot and the recovery period is reduced. Borrie (1953) recommends induction of an artificial pleurisy to prevent recurrence.

Intrapleural fibrinolytic enzymes have been used to prevent organisation of the hæmothorax. Certain strains of streptococci produce a fibrinolysing substance which has been called streptokinase and a desoxyribose nucleoprotein lysing enzyme called streptodornase. These have been used, either singly or together, in the treatment of hæmothorax and empyema. In hæmothorax the main solid constituent of the exudate is fibrin against which streptokinase is particularly active. Experimentally these drugs have no lytic effect on organised fibrous tissue, nor do they cause necrosis of living cells. The optimal time for using these substances has not been fully determined, but their use in the first few days is open to objection on the grounds of precipitating further hæmorrhage by dissolving protective clots. This probably occurred in the treatment of Case 6. Nevertheless, if organisation has taken place to the extent of the formation of fibrous tissue the enzymes will be ineffective. Carr and Robins (1951) consider that 14 days is a satisfactory time to start streptokinase-streptodornase therapy, although Jones and Bigham (1953) suggest that injections should be given early, when it is evident that active hæmorrhage has ceased. Aspiration should be carried out within eight hours and further injections of streptokinase and streptodornase should be given on alternate days until the space is dry or obliterated.

Thoracotomy with decortication of the lung is required when organisation of the layers of fibrin is established and the lung fails to expand. Early operation may be difficult because the organised layer is friable and prolonged delay may allow organisation to be so advanced that stripping is impossible. In cases of traumatic hæmothorax Ogilvie (1950) suggested that the fourth week might be a suitable time.

Finally, intensive physiotherapy is required in all cases. Case 4, who did not have any physiotherapy, had marked flattening and diminution of expansion of the affected side of the chest 18 months after the acute episode. The other six surviving patients, one of whom was seen after five and a half

Patient	*Age*	*Sex*	*Occupation*	*Previous and family history*	*Presenting symptoms*	*Signs*	*Treatment and progress*	*Follow-up*		
								Period	*Clinical*	*Radiography*
1	27	M	Farm worker	Nil	Soreness of chest. Dyspnœa	General condition good. R. hydropneumothorax. X-ray — complete collapse R. lung	Repeated aspiration and blood transfusion. Gradual deterioration and death 44 hrs. from onset. Necropsy: bleeding had occurred from fair-sized artery in ruptured adhesion. Small emphysematous bullæ at both apices	—	—	—
2	45	M	Miner	Pleural effusions at 17 and 43	Breathlessness and coughing. No pain	III. Extreme breathlessness. Large left pleural effusion. Hydropneumothorax revealed by radiography	Aspiration. Total of 2,100 ml. blood removed on four occasions	5½ years	Well and at work	Slight pleural thickening L. side
3	27	M	Mining surveyor	Nil	Pleuritic pain followed by breathlessness and sensation of splashing in chest	Large left hydropneumothorax	Total of 3 litres blood removed on four occasions with air replacement. Transfusion of 2 pints of blood	3½ years	Well	Obliteration L. costophrenic angle. Slight bulla formation R. apex
4	24	M	Machinist	Nil	Pain L. shoulder followed by breathlessness	On third day L. tension pneumothorax with dullness at base	Aspiration of air and blood. Total of 2·8 litres removed. Transfusion of 3 pints blood	1½ years	Well. Flattening of L. chest anteriorly with diminished movement	Normal

5	[illegible]		contractor	at 23	breathlessness. R. pneumothorax diagnosed four weeks before admission	thorax on admission. Confirmed by radiography, but aspiration only carried out on seventeenth day because of increasing fluid	[illegible] fluid increased despite aspiration of 600 ml. blood on two occasions. Further aspirations of 1,500 ml. and 900 ml. followed by recurrence of pneumothorax. Thorascopy performed — slight scarring of apex right lower lobe. Pleural cavity powdered with kaolin and lung re-expanded. Further progress satisfactory	[illegible]	[illegible]	[illegible]
6	18	M	Machinist	Nil	Pleuritic pain and breathlessness. Faintness	R. pleural effusion. Hydropneumothorax revealed by radiography	Aspiration and introduction of streptokinase-streptodornase mixture followed by evidence of further bleeding into the pleural cavity (see Case Report)	1 year	Well	A few pleural peaks on R. diaphragm
7	27	M	Commercial traveller	Nil	Aching pain in R. lower chest anteriorly with breathlessness. Admitted on fourth day	General condition good. R. hydropneumothorax. Tenderness and rigidity of R. side of abdomen with diminished movement	Aspiration on two occasions yielding 1,200 ml. and 450 ml. respectively	1 year	Well	Normal
8	24	M	Miner	Nil	Aching pain in R. shoulder followed by severe pain beneath R. costal margin. Marked dyspnœa. Symptoms persisted for three days with increasing faintness and sweating	Extreme shock. P 132. B.P. unrecordable. R. hydropneumothorax with marked shift of mediastinum to opposite side. Hb. 51%	Rapid transfusion of Dextran followed by 14 pints of blood over four days. Reduction of raised intrapleural pressure. Repeated aspirations. Gradual improvement. Thoracotomy with decortication eighteen days from onset because of clotted hæmothorax	6 mths.	Well	Normal

years, were all well and had no physical abnormality. X-ray of the chest showed a slight pleural shadowing in four out of seven cases.

The mortality of this condition is in the region of 15 per cent. This could be reduced by early diagnosis and adequate treatment.

Summary

In a series of 68 cases of spontaneous pneumothorax admitted to the Royal Victoria Infirmary, Newcastle upon Tyne, in the years 1949-54, eight cases were complicated by bleeding into the pleural cavity and these are reported. One case died and the autopsy findings are described. The other cases have been followed up, the longest period of follow-up being five and a half years.

Difficulties in the diagnosis and management of these cases are discussed. Intrapleural streptokinase-streptodornase mixture was given in one case and evidence is produced to suggest that this precipitated further bleeding. All cases should be in a hospital, where thoracotomy can be carried out if operation becomes necessary as an urgent measure.

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CHLORPROMAZINE IN ASTHMA, CHRONIC BRONCHITIS AND EMPHYSEMA

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Chlorpromazine has among its actions the function of reducing tension without causing depression such as is often seen during prolonged administration of barbiturates. Its sleep-making activity is similar to physiological sleep, in contrast to barbiturate-induced sleep, and its action generally is that of a central sedative, hypnotic and anticonvulsant. Its antihistamine activity is slight.

There are few reports of its use in respiratory disease. Broglie *et al.* (1953) have described their experience with the drug in a number of conditions, including over twenty-five patients admitted to hospital with severe asthma. Initially treatment was by parenteral administration of 25 to 50 mg. of chlorpromazine, commonly combined with 25 mg. of promethazine and 100 mg. of pethidine. The disease was brought under control, usually within two to four days. Robinson and Zuck (1954) have described the effect of a similar intravenous injection in four patients admitted to hospital in status asthmaticus. In each case the outcome was highly satisfactory, although bronchospasm was not relieved immediately, and the relief may have been through adequate sedation rather than a direct antispasmodic action of the drug.

Since the end of 1954 chlorpromazine has been used for appreciable periods in this clinic in fifty-four patients. All patients had some degree of bronchospasm; in thirty-nine the main condition was asthma, in ten chronic bronchitis, and in five emphysema. The age grouping and the severity of the disease are shown in Table 1.

All patients were treated as out-patients. Chlorpromazine was given as the first choice when sedation was indicated. Routine assessments were made of the

Table 1

	Asthma		*Bronchitis*		*Emphysema*	
Age (years):	*M*	*F*	*M*	*F*	*M*	*F*
Under 21	2	1	—	—	—	—
21–40	3	14	—	3	—	—
over 40	5	14	6	1	5	—
Severity:						
Slight	—	2	—	1	—	—
Moderate	5	19	5	2	—	—
Marked	5	8	1	1	5	—
Total treated	10	29	6	4	5	—

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relevant significance of allergic and emotional factors; emotional disturbance was more important in thirty-eight cases and allergic sensitivity in nine; in seven cases both factors were highly significant. The average age of the men was considerably higher than the average age of the women (47 and 38·5 years respectively), and in general the disease among the men was more advanced and chronic.

The initial dose of chlorpromazine was 75 mg. daily, which was often increased to 100 mg. and occasionally to 200 mg. for short periods. When improvement occurred it was manifest within a few days, but maximum benefit was often not obtained for three or four weeks; in general older patients appeared to be slower in responding. Treatment was stopped after three to four weeks if there was then no evidence of improvement. When the response was favourable the drug was continued for periods of up to fifty weeks, but as a rule a point was reached after four to six months when administration could be stopped without recurrence of the original symptoms. Complementary methods of treatment, such as the use of bronchodilators, antibiotics and desensitisation, were employed when indicated. Improvement in the asthma or bronchitis was usually associated with a feeling of well-being, and a lessening of aggression, tension and depression. Frequently the decrease in anxiety was of indirect assistance symptomatically, as when it led to a lessening of smoking with a reduction of cough or to better sleep.

Three patients showed a degree of symptomatic improvement which was immediate and out of all proportion to the general sedating action of the drug.

Case Reports

Case 1. A woman aged fifty-six years who had had asthma for twenty-six years. She had primary ovarian agenesis. She was a tense anxious woman who had attended many hospital out-patient departments and had had treatment during recent years mainly by barbiturates and adrenaline. Skin testing indicated moderate sensitivity to house dust. The symptomatic response to 75 mg. of chlorpromazine daily was immediate. Improvement in her general anxiety and depression occurred slowly over a period of three months. Desensitisation to dust was carried out. After four months the dose of chlorpromazine was reduced to 50 mg., later to 30 mg. daily, and was stopped after nine months; she was having only occasional bouts of asthma which did not increase in frequency.

Case 2. A married woman of forty-five years had suffered from bronchitis for twenty-three years, and for five years also had attacks of asthma, occurring generally on exposure to dust. Skin testing had confirmed a marked allergy to dust, and desensitisation had led to a reduction in the frequency of the asthmatic attacks, which thereafter occurred mainly during phases of emotional tension. However, with the improvement in the asthma the bronchitic symptoms became more prominent, and she was considerably crippled on account of severe cough, dyspnœa and palpitation. She was an unhappy woman, full of complaints. She was given 75 mg. of chlorpromazine daily with dramatic effect. Her troublesome cough cleared up completely and the mucoid sputum disappeared. The change in her attitude was most remarkable; she became cheerful and contented and took up social activities which she had not followed for years. One side effect was that pruritus vulvæ, which had troubled her intermittently for years, disappeared and has not recurred. Administration

of chlorpromazine was continued for seven months. Some acute bronchitic episodes occurred during the winter following its cessation, but were of short duration and of a mild type.

CASE 3. A man aged fifty-four years had had symptoms of emphysema of increasing severity for six years. Bronchitic symptoms were negligible. The blood pressure and an electrocardiograph were normal. Urinary ketosteroids were 2·7 mg. in twenty-four hours. Mentally he was depressed and irritable. He was given 75 mg. of chlorpromazine daily, later increased to 100 mg. daily, and continued at that level, with occasional short periods when the dose was 150 to 200 mg. daily. Improvement in his symptoms was steady. His weight increased, lassitude and weakness passed off and dyspnœa became very much less. He was still rather irritable and depressed, but had periods when his attitude was cheerful and constructive. After ten months he developed symptoms of acute anxiety, but these were not associated with any dyspnœa or respiratory symptoms.

CASE 4. A fifty-eight-year-old woman first had asthma during the summer nine years previously. She had a course of desensitisation at another hospital, and kept well for almost eight years. The asthma recurred in the month of June during a protracted period of emotional strain. When seen the following year she was very tense and depressed, and was having continual severe asthma. Seventy-five mg. of chlorpromazine daily was prescribed, together with actidil and aminophylline, but within forty-eight hours of starting the drugs she passed into status asthmaticus. The chlorpromazine only was stopped, with rapid relief. Four weeks later, when the asthma had subsided, she was again given chlorpromazine and within twenty-four hours was suffering from severe bronchospasm.

The final results of treatment are shown in Table 2.

TABLE 2

	Asthma		*Bronchitis*		*Emphysema*		*Total*	
Symptomatic improvement:	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*
Marked	4	12	2	2	2	—	8	14
Slight	2	3	2	1	2	—	6	4
No change	4	9	2	1	1	—	7	10
Worse	—	5	—	—	—	—	—	5

Symptomatic improvement occurred in twenty-four of thirty-eight cases in which the emotional factor was more significant than the allergic, and in four of nine in which the allergic factor was predominant. Some patients showed an improvement in outlook and attitude which was not accompanied by any relief of bronchospasm or other respiratory symptoms. There was little difference in the results between the two sexes. Improvement occurred in the three patients with early disease; seventeen of thirty-one whose disease was moderately advanced, and twelve of twenty with far advanced disease. Age also had very little effect on the result of treatment, except that results were poorer when organic changes were more advanced. There were no serious toxic reactions. Some patients complained of unpleasant subjective feelings or unpleasant dreams, which as a rule were temporary, but in two cases necessitated termination of administration.

The favourable action of chlorpromazine appeared to be mainly an indirect one through the lessening of emotional tension. The effect was usually more striking when anxiety was long standing and related to deep-seated emotional conflict than when acute and caused by immediate environmental circumstances. In predominantly allergic cases there sometimes appeared to be a lessening in the reactions to known allergens such as dust, and in this group also chlorpromazine often accentuated the effect of antihistamines.

Summary

Chlorpromazine was given over prolonged periods to fifty-four patients with bronchospasm due to asthma, chronic bronchitis or emphysema. Symptomatic improvement occurred in 59 per cent. of all cases; it was most frequent in the group in which emotional factors were predominant. Side effects were few and unobtrusive.

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THE UNUSUAL OCCURRENCE OF AN ACID-FAST "SAPROPHYTE" AND *SALM. TYPHI-MURIUM* IN ASSOCIATION WITH A PULMONARY LESION

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Though mammalian tubercle bacilli are the most important mycobacteria in pulmonary disease, sometimes, in routine sputum cultures, other acid-fast bacilli are found which appear to be associated with a pulmonary lesion. Of these, cases attributable to avian tubercle bacilli are few in number (Feldman, 1938; Bradbury and Young, 1946; and Dragsted, 1949), the majority of the positive isolations from sputum being strains of unclassifiable acid-fast bacilli generally referred to as "saprophytic" or "atypical" mycobacteria.

Tarshis and Frisch (1952) and Timpe and Runyon (1954) have examined many such strains from human sources and found that most of them formed colonies that were smooth, soft, and more or less yellow. In general their growth requirements and rate of growth on primary isolation resembled those of tubercle bacilli, but they had little or no virulence for guinea-pigs. In most of the cases reported on by other authors, similar acid-fast "saprophytes" have been described. Feldman *et al.* (1943) isolated a mycobacterium from the sputum of a patient over a period of many years. In their detailed bacteriological study of the organism it was noted that the acid-fast bacillus had many features in common with the avian tubercle bacillus.

On the basis of colony features and mouse pathogenicity tests, Timpe and Runyon (1954) have divided the acid-fast "saprophytes" forming smooth colonies into two groups, one of which is pathogenic for mice while the other is non-pathogenic. A third group, also pathogenic for mice, resembles mammalian tubercle bacilli in colonial appearance. Young (1955) has reported on a case of pulmonary disease due to a similar rough strain of acid-fast "saprophyte."

In the case presented here, we have observed for over three years the frequent occurrence of a chromogenic "saprophytic" mycobacterium in the sputum of a patient suspected of having pulmonary tuberculosis, and, in addition, we have on many occasions found *Salm. typhi-murium* in the sputum of the same patient. Though organisms of the *Salmonella* group have been isolated from diverse pathological material we have traced only three references to the isolation of salmonellæ from sputum. Thus Seligmann, Saphra and Wassermann (1943) in an analysis of 1,000 cases bacteriologically examined at the New York Salmonella Centre mention the isolation of *Salm. newport* from the sputum in one case. Colbeck and Neisser (1948) record the finding of *Salm. typhi-murium* in the sputum of an asthmatic, and Ingegno *et al.* (1948) the isolation of *Salm. montevideo* from a patient suffering from broncho-pneumonia.

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Case Report

A man aged 42, originally a miner, was admitted to hospital in July 1951 acutely ill with vomiting, diarrhœa and abdominal pain. No intestinal pathogens were found. However, an X-ray examination revealed opacities in the left upper zone of the lung and a diagnosis of pulmonary tuberculosis was made. There was no previous history of this disease, though in 1936 he was ill with pleurisy and pneumonia and shortly afterwards developed symptoms of a gradually progressive nervous disease later diagnosed as disseminated sclerosis. From 1949 onwards he had complained of recurrent bouts of diarrhœa.

When seen at a Chest Clinic in August 1951 the patient still complained of occasional diarrhœa but, apart from slight cough with rather scanty but purulent sputum, he seemed to be fairly well. Radiologically, however, there were fibrotic changes in the left upper lung field and a few discrete opacities in the first right interspace (Fig. 1). The first sputum sent for bacteriological examination, though no acid-fast bacilli were seen microscopically, when cultured on Löwenstein-Jensen medium, yielded a luxuriant growth of butyrous, yellow colonies of acid- and alcohol-fast bacilli. In three further specimens of sputum examined in 1951, swollen and vacuolated acid-fast bacilli were seen on microscopical examination of smears in two; all three gave rise on culture, after about three weeks' incubation, to a growth of yellow or cream coloured smooth soft colonies of acid-fast bacilli similar to those obtained in the first instance. Two of the sputa were inoculated each into two guinea-pigs. One animal killed after ten weeks and the other after three months showed no evidence of tuberculosis.

The patient was admitted to hospital for a short period in February 1952, and Mantoux tests were performed with P.P.D. tuberculins prepared from human and avian strains of tubercle bacilli. With a dilution of mammalian tuberculin corresponding to 1/10,000 O.T. there was an induration 14 mm. in diameter, but only a very slight skin reaction was obtained with a dilution of 1/1,000 avian tuberculin. As the patient still complained of bouts of diarrhœa a specimen of fæces was examined and *Salm. typhi-murium* was isolated. Also, by the usual cultural methods for the isolation of tubercle bacilli from fæces, the acid-fast " saprophyte " was isolated. A course of chloromycetin, 2 g. daily for ten days, failed to eradicate the *Salm. typhi-murium*. The patient was then discharged from hospital but kept under observation at the chest clinic.

The results of sputum and fæces examinations for mycobacteria, from 1951 to 1954, are shown in Table I. Altogether, of thirty-five sputa examined, the acid-fast "saprophyte" was cultured from thirty-three and acid-fast bacilli were seen, on microscopical examination, in eight. Eighteen of the sputum specimens (B) were inoculated also into guinea-pigs in attempts to find mammalian tubercle bacilli. Some of the animals were killed after six weeks and some after three months, but no evidence of tuberculosis was found and no local lesions were seen. Cultures of the spleen did not produce a growth of acid-fast bacilli. Six of the guinea-pigs were tested with old tuberculin (B.W.) prepared from mammalian tubercle bacilli and a glycerine extract was prepared from a culture of the acid-fast " saprophyte." In all cases a positive skin reaction was obtained with a dilution of 1/1,000 glycerine extract prepared from the acid-fast " saprophyte," though with a dilution of 1/100 O.T. (B.W.) the tuberculin test was negative. Control guinea-pigs showed no reaction with 1/10 and 1/100 of the extract prepared from the acid-fast " saprophyte."

In November 1952 many Gram-negative bacilli were seen in Gram-stained films of the sputum and, on direct culture on blood-agar and MacConkey solid

PLATE XVIII

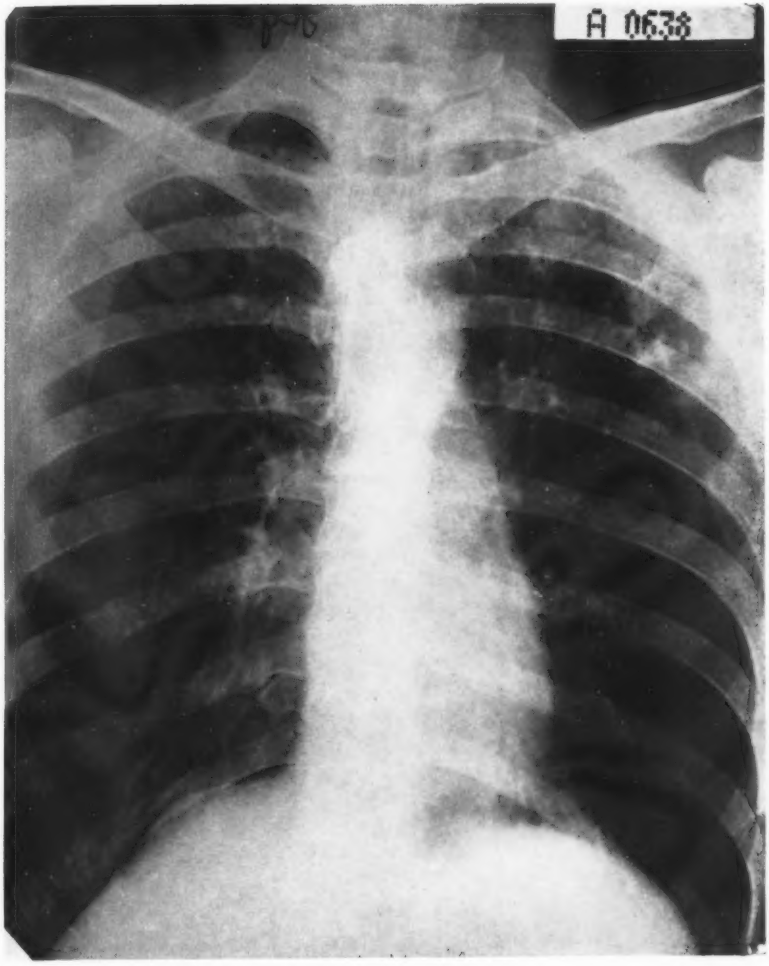

FIG. 1.—Radiograph of 30th August, 1951, showing opacities in the left upper zone and first right interspace.

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TABLE I.—RESULTS OF SPUTUM AND FÆCES EXAMINATIONS DURING 1951–54
Positive cultures, +; positive smears, (+); guinea-pig inoculations, B; negative cultures, —.

Date	Sputum		Fæces	
	Acid-fast "saprophyte"	*Salm. typhi-murium*	*Acid-fast "saprophyte"*	*Salm. typhi-murium*
1951				
September	+			
October	+			
November	+ (+) B			
December	+ (+) B			
1952				
January	+			
February	+		+	+
,,	+B			
,,	+ (+) B			
,,	+			
,,	+ B			
,,	+ (+) B			
March	+ B			
July	+			
September	+ (+) B			
October	+ (+) B			
November	+ B	+		
December	+ (+) B	+	+	+
,,	+ B	+	+	+
,,	+ (+) B	+		
,,	+ B	+		
,,	+ B	+		
,,	+ B	+		
,,	+ B	+		
1953				
January	+	+		
,, ...	+			
February	+	—		
March	—	+		—
,, ...				—
June	+	+		—
July	— B	+		+
October	+	+		+
November	+	—		+
,,				—
,,				—
,,				—
,,				—
December	+	—		—
,,	+	—		—
1954				
January	+	—		—
March				—
November				—
December	+	—		

medium, *Salm. typhi-murium** was isolated. Special care was taken in the collection of seven sputa during December, 1952, and all of them yielded a growth of *Salm. typhi-murium*. A number of attempts were made to isolate *Salm. typhi-murium* on MacConkey plates used as cough plates and on one occasion three colonies of the salmonella were found. The results of examinations of sputum and fæces for *Salm. typhi-murium* during 1952 and 1953 are shown in Table I.

In December 1952 the patient was given a course of streptomycin, even though the " saprophytes " were found to be sensitive to streptomycin only at a concentration of 4 μg. per ml. The course consisted of daily injections of 1 g. of streptomycin for thirty days followed by 1 g. on alternate days up to a total dose of 36 g. The treatment produced no change in the radiological picture, which, indeed, has not apparently altered since 1951. About the end of October 1953 the patient was treated with terramycin given orally, 2 g. daily over a period of ten days. After completion of the course *Salm. typhi-murium* was no longer found in the sputum and fæces, though the acid-fast " saprophyte " continued to be isolated from the sputum.

Bacteriology

Morphology. The myco-bacteria were aerobic, non-motile, acid- and alcohol-fast and Gram-positive. On culture they were usually considerably longer than tubercle bacilli and showed much beading. Pleomorphism was common. No branching was seen. In direct films of sputum the bacilli were greatly swollen and vacuolated.

Cultural Characteristics

Growth was fairly rapid on a variety of media at 37° C. On Löwenstein-Jensen medium without glycerine there was a confluent soft growth after eleven days' incubation. With the addition of 5 per cent. glycerine a profuse yellow or cream-coloured growth was obtained in five to seven days. The addition of glycerine also enhanced the growth on Dorset's egg medium, Loeffler's medium and nutrient agar. With potato and 5 per cent. glycerine a few colonies appeared at fourteen days, and at three weeks there was a luxuriant growth of large yellow discrete colonies. Without glycerine there was no growth after six weeks' incubation. On blood agar there was a fine grey confluent growth at eleven days. On Dubos agar the colonies were small with no sign of cord formation. In Dubos fluid medium growth was poor in comparison with human tubercle bacilli. In the synthetic medium of Dorset and Henley growth was luxuriant in a few days.

At room temperature the acid-fast " saprophyte " grew very poorly or not at all after six weeks. At 44° C. on Löwenstein-Jensen medium with glycerine there was a moderate growth after three weeks' incubation.

Pathogenicity

Different doses (wet weight) of ten-day-old cultures were inoculated into various animals. The details and results are summarised in Table II.

Guinea-pigs. One animal developed a local abscess after nine days which regressed after fifteen days. The abscess occurred at the site of inoculation and numerous acid-fast bacilli were seen in Z.N. smears of the pus. No evidence of

* Confirmed by the Salmonella Reference Laboratory.

TABLE II.—RESULTS OF PATHOGENICITY TESTS

I.M., intramuscular inoculation; I.V., intravenous inoculation; I.P., intraperitoneal inoculation; K, killed; D, died; G.L., focal granulomatous lesions; N.F., granulomata with necrotic foci; A.F.B., acid-fast bacilli.

Animal species	*No.*	*Inoculum mg.*	*Route of inoculation*	*Days after inoculation*	*Macroscopic lesions*	*Histology*			
						Lung	*Liver*	*Spleen*	*Gland*
Guinea-pig	1	1	I.M.	150 K	None				
	2	1	I.M.	150 K	None				
Rabbit	1	50	I.V.	70 D	None				
	2	1	I.V.	90 K	None	Nil	Nil	Nil	
	3	1·1	I.V.	21 D	None	G.L.	G.L.	N.F.	
	4	0·01	I.V.	150 K	None				
	5	0·001	I.V.	150 K	None				
Hen	1	10	I.P.	90 K	None				
	2	0·5	I.V.	90 K	None				
Mouse (white	1	0·5	I.P.	35 K	Enlarged mesenteric glands			A.F.B.	N.F. A.F.B.
	2	0·5	I.P.	35 K	None				
	3	0·5	I.P.	56 K	None	G.L.	Nil	Nil	Nil
	4	0·5	I.P.	56 K	Enlarged mesenteric glands	G.L. A.F.B.	Nil	A.F.B.	N.F. A.F.B.
	5	0·5	I.P.	77 K	Enlarged mesenteric glands	G.L. A.F.B.	Nil	Nil	N.F. A.F.B.
	6	0·5	I.P.	77 K	Adhesion bowel and liver Enlarged glands and spleen	G.L. A.F.B.	A.F.B.	A.F.B.	N.F. A.F.B.
Mouse (brown	7	0·1	I.P.	77 K	Enlarged mesenteric glands	G.L. A.F.B.	Nil	Nil	N.F. A.F.B.

disease was found at post-mortem examination. Splenic cultures were also negative.

Rabbits. Variable results were obtained with rabbits. One died ten weeks after inoculation. No macroscopic lesions were noted but numerous acid-fast bacilli were seen in smears of lung, liver and spleen and a growth of the acid-fast "saprophyte" was obtained on culture. A second rabbit died three weeks after inoculation and again no macroscopic lesions were found at post-mortem examination though acid-fast bacilli were seen in smears of spleen, lung, liver and kidney. Histological examination showed the presence of small granulomata in liver and lung. In the spleen there were a small number of small multinucleated cells and tiny foci of necrosis. The other three rabbits showed no clinical evidence of disease. No lesions were seen at post-mortem examination and no

sections were made. Splenic cultures were negative for two of the animals, but with rabbit No. 5 a growth of the acid-fast " saprophyte " was obtained.

Hens. The acid-fast " saprophyte " did not produce disease in two young hens. No lesions were found and no organisms were seen in smears of tissues or recovered from cultures of the spleen.

Mice. Of seven mice, killed and examined at different intervals of time after inoculation, five showed enlargement of the mesenteric lymph glands. In mouse No. 6 the glands were necrotic and smears showed large numbers of acid-fast bacilli. There was also an adherent mass incorporating adjacent portions of liver and bowel and enlarged necrotic glands. The spleen was enlarged and numerous acid-fast bacilli were seen in smears of spleen, liver and lung as well as glands.

Histology. Sections of the lungs of five of the mice were examined and all showed granulomatous foci. Acid-fast bacilli were seen in most of the sections. In the mesenteric glands there were granulomata with necrotic centres and numerous acid-fast bacilli. No microscopic lesions were seen in spleen, liver or kidney, though acid-fast bacilli were present, sometimes, in spleen and liver.

Discussion

The strain of acid-fast bacillus which we have described appears to be similar to many reported strains of acid-fast " saprophytes " found in association with pulmonary disease. Without knowledge of their origin it is difficult to know what to call them and, so far, no satisfactory term has been found for them. They form a group that has many of the cultural characteristics of avian tubercle bacilli, but in which the production of a yellow pigment is usually such a striking feature as to merit the description of chromogenic acid-fast bacilli. However, like Feldman *et al.* (1943), we have found pigment production to be variable with our strain. Pathogenicity tests with different animal species were, more or less, in agreement with the results obtained by Feldman *et al.* (1943), Timpe and Runyon (1954), Pollak and Buhler (1955), and Robbins *et al.* (1955). The organism was not virulent for guinea-pigs or fowls and variable results were obtained with rabbits. Experimental infection of mice did not produce the gross pulmonary lesions found by Timpe and Runyon with his Group I organisms, but there was substantial evidence that the organism was capable of producing disease in mice, particularly in lung tissue and lymph glands.

The numerous positive isolations of these acid-fast " saprophytes " from cases of pulmonary disease leave no doubt that they can be troublesome in the diagnosis of tuberculosis. Though the majority of the strains have been isolated from patients with old tuberculous lesions, in some instances similar acid-fast " saprophytes " have been incriminated as the causative organisms of pulmonary disease. The ætiology in our case is obscured, to some extent, by the finding of *Salm. typhi-murium* in the sputum as well as the acid-fast " saprophyte." Before the patient came under observation he was a chronic invalid suffering from disseminated sclerosis which apparently developed shortly after a respiratory illness fifteen years previously. In July 1948 he had a clinical examination in hospital, and in view of his previous history it is highly improbable that a pulmonary lesion would pass unnoticed. It seems probable, therefore, that

the pulmonary infection was acquired between 1948 and 1951. During this period he attended hospital as an out-patient, and from 1949 his main complaint was of frequent bouts of diarrhœa which were thought to be of nervous origin. He was seen at the hospital in June 1951, and though he was still complaining of diarrhœa nothing else of significance was noted. In July of the same year he was admitted to hospital acutely ill with abdominal pain, vomiting and diarrhœa—symptoms suggestive of a salmonella enteritis. As acid-fast "saprophytes" were found in the sputum soon after this illness they presumably preceded *Salm. typhi-murium* in lung lesion. The pulmonary disease has now run a mild course for over four years and the radiological picture has not changed. All attempts to demonstrate the presence of tubercle bacilli have failed, though the acid-fast "saprophyte" has been repeatedly isolated from sputum specimens. It seems justifiable, therefore, to assume that the lung lesion was due to a primary infection of the acid-fast "saprophyte."

In old tuberculous lesions, mycobacteria of this group are probably fortuitous invaders but, nevertheless, they appear to be endowed with a degree of virulence sufficient to enable them to establish themselves and persist for long periods. In cases of achalasia of the cardia, according to Gibson (1953), there may be a synergism of aspirated fat and acid-fast "saprophytes" with consequent enhancement of virulence. Whether in other cases of primary infection the "saprophytic" mycobacteria are capable of initiating a lung lesion is not known. There may be, of course, differences in virulence between different strains. It is possible, also, that they may require a nidus of previously damaged lung tissue in which they can lodge before an infection can become established. Other factors such as lowered resistance due to debility, applicable in our case, must be considered. Enhancement of virulence by concomitant infection with other pathogens cannot be disregarded even though Timpe and Runyon were unable to find any evidence for this in any of the earlier cases. In that respect our case must be unique in that another pathogen—*Salm. typhi-murium*—was found in association with the acid-fast "saprophyte." It is doubtful, however, whether the dual infection in this instance led to any appreciable enhancement of virulence.

Summary

A case simulating pulmonary tuberculosis, due to a chromogenic acid-fast "saprophyte," is reported. The occurrence, also, of *Salm. typhi-murium* in the sputum is believed to have resulted from a superinfection. The relationship of the acid-fast bacillus isolated to similar strains of acid-fast "saprophytes," and the rôle of these organisms in pulmonary infections, are discussed.

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PEPTIC ULCER AND PULMONARY TUBERCULOSIS

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The apparently high incidence of pulmonary tuberculosis in patients followed up after partial gastrectomy has been commented on by Pulvertaft (1952), Warthin (1953) and Pearson (1954).

As a result of these reports, the impression has gained ground that partial gastrectomy gives rise to an increased risk of the subsequent development of pulmonary tuberculosis or the reactivation of previously quiescent disease. In view of the influence which this fear may justly or otherwise exert on the treatment of peptic ulcer by surgery, especially in cases where there is knowledge of a pre-existing tuberculous lesion, an attempt has been made to examine the problem by reviewing the patients attending the Hammersmith Chest Clinic who have a history of both pulmonary tuberculosis and peptic ulcer.

Previous articles have stressed the importance of partial gastrectomy in relation to pulmonary tuberculosis by concentrating on the follow-up of patients treated surgically for peptic ulcer. However, little attention has been paid to the relationship of medically treated peptic ulcer to pulmonary tuberculosis. It would seem that a useful comparison might be made between these two forms of treatment for peptic ulcer in relation to their effect on the clinical course of pulmonary tuberculosis.

Material

There are 1,386 patients suffering from pulmonary tuberculosis attending the Hammersmith Chest Clinic. Of these 46 (3·3 per cent.) have had treatment for peptic ulcer and the records of those patients who have died since 1950 yield 3 more. Eleven patients whose peptic ulcers are of less than two years' duration have been excluded because of the shortness of the follow-up period. One other with a gastro-enterostomy has also been excluded to simplify comparison. This leaves a total of 37 patients for consideration, of whom 16 were treated by partial gastrectomy and 21 received medical treatment for peptic ulcer.

In the surgically treated group of 16 cases, the diagnosis of pulmonary tuberculosis was confirmed bacteriologically in 13 of the patients, while in the remainder the radiological findings were typical of inactive tuberculosis and included calcification. In every case the diagnosis of peptic ulcer (9 duodenal and 7 gastric) was confirmed by pre-operative barium meal or by the findings at operation. There are 14 men and 2 women, all over 40 years of age at the time of operation. Nine patients had a Polya and 7 had a Billroth 1 type of partial gastrectomy.

In the medically treated group of 21 cases the diagnosis of pulmonary tuberculosis was confirmed bacteriologically in 15 of the patients and in the

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others the diagnosis was made on radiological grounds. In every case the diagnosis of peptic ulcer (15 duodenal and 6 gastric) was confirmed by barium meal or by the findings at operative repair of a perforation. There are 18 men and 3 women and the majority (18 out of 21) were over the age of 40 when their peptic ulcers were diagnosed. All the patients received medical treatment—11 in hospital and the remainder as out-patients. Seven patients had surgical repair of a perforation during their history of chronic peptic ulcer.

Method

Direct comparison between the surgically and medically treated groups may be made in two ways:

1. Those patients who are known to have had pulmonary tuberculosis at the time when their peptic ulcers were treated can be studied by comparing the proportion in each group who subsequently showed reactivation of their tuberculosis.

2. In those patients who developed pulmonary tuberculosis subsequent to peptic ulceration, it is possible to compare the time intervals in each group between the treatment for peptic ulcer and the onset of tuberculosis.

Although the surgically and medically treated groups are not matched, the case records show that they approximate very closely in respect of the age and sex distribution, the extent of pulmonary disease and the family and contact history of pulmonary tuberculosis. It is probable that the surgical group contains those patients with the more severe and troublesome peptic ulcers.

Results

(See Tables 1 and 2)

1. *Patients known to have had pulmonary tuberculosis when their peptic ulcers were treated.*

Of the 6 patients treated surgically who are known to have had pulmonary tuberculosis at the time of partial gastrectomy, 4 had a relapse of their chest lesions. Similarly, of the 12 patients with pre-existing tuberculous lesions who received medical treatment for peptic ulcer, 6 suffered reactivation of their tuberculosis. The average follow-up period in both groups is similar (four and a half years).

2. *Patients who developed pulmonary tuberculosis after treatment for peptic ulcer.*

In the surgically treated group of 10 patients the average time interval between partial gastrectomy and the onset of pulmonary tuberculosis is 6 years (1, 2, 1, 4, 4, 7, 24, 1, 8, 10 years). In the medically treated group of 9 patients the average time interval is also 6 years (2, 3, 4, 6, 4, 12, 8, 12, 4 years).

Discussion

Previous investigations of pulmonary tuberculosis following partial gastrectomy were made either by studying the mortality from pulmonary tuberculosis in a follow-up series of patients operated on for peptic ulcer, or by analysing the morbidity of pulmonary tuberculosis following partial gastrectomy. The latter method would seem to give the more detailed information.

Pulvertaft (1952) and Swynnerton and Tanner (1953) based their investiga-

TABLE 1.—PARTIAL GASTRECTOMY CASES

No.	Sex	Age in 1955 or at death	Operation for peptic ulcer	Diagnosis of pulmonary tuberculosis	Activity of pulmonary tuberculosis at time of partial gastrectomy	Course of pulmonary tuberculosis after partial gastrectomy
1	M	49	1953 Polya—D.U.	1954 (Sputum +ve)	Not known	1954 onset
2	M	46	1949 Billroth 1—D.U.	1946 (Sputum +ve)	Active	1950 exacerbation
3	M	55	1950 Polya—G.U.	1952 (Sputum +ve)	Not known	1952 onset
4	F	52	1953 Billroth 1—G.U.	1954 (Sputum −ve)	Not known	1954 onset
5	M	52	1945 Billroth 1—D.U.	1949 (Sputum +ve)	No tuberculosis	1949 onset
6	M	50	1947 Polya—D.U.	1951 (Sputum +ve)	No tuberculosis	1951 onset
7	M	76	1953 Billroth 1—G.U.	1943 (Sputum −ve)	Quiescent	No change
8	M	56	1950 Polya—D.U.	1942 (Sputum +ve)	Quiescent	1951 exacerbation
9	M	61	1945 Billroth 1—G.U.	1952 (Sputum +ve)	No tuberculosis	1952 onset
10	M	67	1929 Polya—G.U.	1953 (Sputum +ve)	No tuberculosis	1953 onset
11	M	43	1952 Billroth 1—D.U.	1944 (Sputum +ve)	Quiescent	No change
12	M	51	1953 Polya—D.U.	1954 (Sputum −ve)	Not known	1954 onset
13	M	52	1944 Polya—D.U.	1952 (Sputum +ve)	No tuberculosis	1952 onset
14	M	65	1949 Polya—G.U.	1948 (Sputum +ve)	Quiescent	1949 death following exacerbation
15	M	73	1944 Billroth 1—G.U.	1954 (Sputum +ve)	Not known	1954 onset
16	F	47	1949 Polya—D.U.	1944 (Sputum +ve)	Quiescent	1953 exacerbation

TABLE 2.—MEDICALLY TREATED CASES

No.	*Sex*	*Age in 1955 or at death*	*Diagnosis of peptic ulcer*	*Diagnosis of pulmonary tuberculosis*	*Activity of pulmonary tuberculosis at commencement of medical treatment for peptic ulcer*	*Course of pulmonary tuberculosis after medical treatment for peptic ulcer*
1	M	50	1951 Ba.Meal—D.U.	1948 (Sputum +ve)	Quiescent	1954 exacerbation
2	M	67	1953 Ba.Meal—D.U.	1953 (Sputum −ve)	Quiescent	No change
3	M	50	1952 Ba.Meal—D.U.	1951 (Sputum +ve)	Quiescent	No change
4	M	58	1951 Perforation—G.U.	1953 (Sputum −ve)	Not known	1953 onset
5	F	60	1950 Ba.Meal—D.U.	1944 (Sputum +ve)	Quiescent	1953 exacerbation
6	M	38	1943 Perforation—D.U.	1946 (Sputum +ve)	Not known	1946 onset
7	M	52	1948 Perforation—D.U.	1952 (Sputum −ve)	Not known	1952 onset
8	M	61	1952 Ba.Meal—G.U.	1951 (Sputum −ve)	Quiescent	No change
9	M	58	1951 Ba.Meal—D.U.	1944 (Sputum +ve)	Quiescent	1951 exacerbation
10	M	49	1948 Ba.Meal—D.U.	1947 (Sputum +ve)	Quiescent	No change
11	M	39	1946 Perforation—D.U.	1952 (Sputum +ve)	Not known	1952 onset
12	F	51	1948 Ba.Meal—D.U.	1945 (Sputum −ve)	Quiescent	No change
13	F	50	1951 Ba.Meal—G.U.	1945 (Sputum +ve)	Active	1951 exacerbation
14	M	58	1940 Ba.Meal—D.U.	1944 (Sputum +ve)	No tuberculosis	1944 onset
15	M	61	1939 Ba.Meal—G.U.	1951 (Sputum +ve)	No tuberculosis	1951 onset
16	M	56	1946 Perforation—G.U.	1954 (Sputum +ve)	Not known	1954 onset
17	M	54	1941 Perforation—G.U.	1953 (Sputum −ve)	Not known	1953 onset
18	M	46	1945 Ba.Meal—D.U.	1943 (Sputum +ve)	Quiescent	1951 death following exacerbation
19	M	71	1951 Perforation—D.U.	1943 (Sputum +ve)	Active	1951 death following exacerbation
20	M	45	1953 Ba.Meal—D.U.	1939 (Sputum +ve)	Quiescent	No change
21	M	60	1951 Ba.Meal—D.U.	1955 (Sputum +ve)	No tuberculosis	1955 onset

tions on mortality figures, but their conclusions differed. Pulvertaft followed up 632 patients who had had a partial gastrectomy and reported that 7 cases died of pulmonary tuberculosis and 1 of tuberculous meningitis. Two of these 7 cases were known to have pre-existing pulmonary tuberculosis. In addition 2 other cases subsequently developed pulmonary tuberculosis. Comment was made on the high incidence of pulmonary tuberculosis, but it was not stated how many of the patients had pre-operative chest X-rays so that the true incidence remains obscure. Swynnerton and Tanner compared the results of surgical and medical treatment for peptic ulcer and found that, in a series of 233 patients followed up after partial gastrectomy for chronic gastric ulcer, 6 men died of pulmonary tuberculosis and 1 woman died of Addison's disease, while another subsequently developed pulmonary tuberculosis. In their other series of 256 medically treated cases, 3 men subsequently died of pulmonary tuberculosis, in only 1 of whom was the diagnosis recorded at the time of admission for gastric treatment. They considered that the evidence concerning an increased risk of pulmonary tuberculosis following gastrectomy was inconclusive.

Warthin and Pearson based their studies on morbidity results. Warthin reported 7 patients out of a series of 356 partial gastrectomies who subsequently developed active pulmonary tuberculosis. Six of these were known to have pulmonary tuberculosis of varying degrees of activity at the time of operation (1 active, 2 doubtful and 3 inactive). It is not stated how many of the remaining 349 had pre-existing tuberculous chest lesions at the time of gastrectomy and therefore the incidence of reactivation of quiescent pulmonary tuberculosis cannot be assessed. Pearson selected 11 patients for study who developed pulmonary tuberculosis following partial gastrectomy, in only 4 of whom was there any evidence of tuberculosis at the time of operation. He suggested that it would be useful if a comparison were made with a similar group treated medically.

Our study of the problem is based on morbidity figures and a comparison of surgically and medically treated patients. Although the number of patients analysed is small, the results suggest, whatever the effect of chronic peptic ulcer on pulmonary tuberculosis, that patients who are treated medically fare little better in respect of their tuberculosis than those who undergo partial gastrectomy. It is questionable whether the fear of advising partial gastrectomy for patients known to have tuberculous lesions may have influenced these results. However, this is unlikely because the majority of the patients had their peptic ulcer treated before Pulvertaft's report was published.

Johnson (1954) reviewed the occurrence of post-gastrectomy symptoms following partial gastrectomy by the Polya and the Billroth 1 type of operation. These included "dumping," bilious regurgitation, abdominal colic, asthenia and inability to eat enough food to maintain body weight. He stated that, in the immediate post-operative period, patients who have had gastrectomies pass into a phase of negative nitrogen balance during which they lose 7 to 14 lb. in body weight. Many recover their pre-operative weight in the course of months or years, but few ever return to the weight they were before they were affected by ulcer.

Pearson stated that 6 of the 11 patients who subsequently developed pul-

monary tuberculosis suffered from post-gastrectomy symptoms leading to weight loss. He suggested that long-standing malnutrition had culminated in a tuberculous infection. Pulvertaft and Warthin also suggested that weight loss following operation was a contributory factor.

In our series of 16 patients treated by partial gastrectomy, 5 (cases No. 1, 3, 5, 7, 11) had moderate or severe post-gastrectomy symptoms with failure to regain their pre-operative weight and 3 of these patients (cases No. 1, 3, 5) subsequently developed pulmonary tuberculosis, while the two with quiescent lesions remained unchanged. Of the remaining 11 patients who had either mild or no post-gastrectomy symptoms, all regained their pre-operative weight with the exception of 2 (cases No. 8 and 14), but 7 of the patients subsequently developed pulmonary tuberculosis and the 4 others had an exacerbation of their quiescent chest lesions. These figures do not support the hypothesis that it is weight loss due to malnutrition following partial gastrectomy which is responsible for the subsequent development of pulmonary tuberculosis or the reactivation of quiescent disease.

Summary

1. Sixteen cases of pulmonary tuberculosis who have undergone partial gastrectomy for peptic ulceration are analysed and compared with 21 cases of peptic ulcer treated medically.

2. The possible effect of weight loss is discussed.

3. The conclusion is reached that any adverse effect which peptic ulcer may have on pulmonary tuberculosis is unlikely to be much increased by partial gastrectomy.

We wish to thank Dr. Peter Stradling for his permission to publish the details of the cases and for his helpful advice in preparing this article.

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THROMBOCYTOPENIC PURPURA IN TUBERCULOSIS

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The occurrence of thrombocytopenic purpura in tuberculosis would appear to be relatively rare, for though it is mentioned in many textbooks under the differential diagnosis of purpura, we could only find 32 cases reported in the literature. According to Villa, Bessaud and Rivet were the first to describe the occurrence of purpura in tuberculosis. In their opinion it was most often seen in the following forms of the disease: miliary, meningitic, genito-urinary, and in tuberculosis involving the lymphatic glands and the suprarenals. They considered that this rash occurred only in fulminant cases. In 1910 Jona reported 5 cases in which he believed that the purpura was due to stasis, thrombosis and sclerosis of the arteries produced by circulating tuberculous toxins.

A further 4 cases were described in 1924 (Pratsicas). The author believed that the hæmorrhagic rash was due to emboli in two of the cases, and to disseminated miliary tuberculosis in a third.

In 1931 Kellert reported a case in which splenectomy had been carried out for thrombocytopenic purpura, the patient making a good recovery. Subsequent histological examination of the spleen revealed that its substance was composed largely of miliary tubercles. An occasional acid-fast bacillus was also found. More recently Gouley has suggested that tuberculosis of the bone marrow is almost certainly a factor in the production of thrombocytopenic purpura in tuberculous patients.

Ellman and Johnson (1952) report 1 case, give a review of the subject and conclude that tuberculosis may cause purpura in various ways; in some there is allergy to tuberculo-protein, in others hypersplenism is the cause, and in a few there is direct infiltration or depression of the bone marrow.

We record here two further cases of thrombocytopenic purpura, which in both patients was the presenting symptom of their tuberculosis.

Case 1. A woman of 20 was admitted to hospital complaining of general malaise and purpuric spots over the body which had been appearing in crops during the last twelve days. She had experienced a few, small epistaxes during the same period. On examination her general condition was good, temperature normal. The mucous membranes appeared pale. There was a hæmorrhagic rash over the whole body, the lesions varying in size from minute petechiæ to large ecchymoses. A few purpuric spots were also seen in the buccal mucosa. No abnormalities were detected in the respiratory or cardio-vascular systems. The blood pressure was 130/80. The spleen and liver were not palpable.

Investigations: Hæmoglobin 72 per cent. White cell count 4,000 per c.mm. (Neutrophils 3,760, Lymphocytes 240). Platelet count: 10,000 per c.mm.

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Bleeding time—in excess of 20 minutes (Ivy). Clotting time 6 minutes (Lee and White). Blood sedimentation rate 15 mm. in the first hour (Wintrobe). Urine—no abnormality detected; blood urea—24 mg. per cent.

Bone marrow was obtained by sternal puncture, and gave the following results:

	Per cent.		Per cent.
Promyelocytes	1·0	Lymphocytes	13·5
Neutrophil band cells	15·0	Monocytes	3·0
Eosinophil band cells	0·5	Pronormoblasts	0·5
Neutrophil myelocytes	8·5	Basophilic normoblasts	2·0
Neutrophil segmented	15·5	Polychromatic normoblasts	18·5
Eosinophil segmented	2·5	Orthochromatic normoblasts	11·5
Basophil myelocytes	0·5	Smear cells	5·0
Blast cells	0·5	Cells in mitosis	2·0

A few megakaryocytes were seen.

X-ray of the chest showed diffuse mottling distributed throughout both lung fields, consistent with the diagnosis of miliary tuberculosis. Mantoux test 1 : 1,000—negative.

On the third day after admission the patient began to menstruate, losing rather heavily. Four days after admission, with the platelet count less than 10,000 per c.mm., splenectomy was performed, the patient making an uneventful recovery. The platelet count rose to 43,000 per c.mm. twelve hours after the operation, and to 120,000 the following day. The spleen weighed 120 g. and showed no macroscopic abnormality. Section, however, showed a few caseating tubercles scattered throughout the pulp.

The patient received a course of Streptomycin and PAS and when last seen, eight months after the operation, her general condition was excellent. X-ray of the chest showed no evidence of abnormality, the hæmoglobin was 93 per cent., white cell count 7,200 per c.mm., platelets 281,000 per c.mm., and the blood sedimentation rate 4 mm. in one hour. The Mantoux test 1 : 100 was positive.

Case 2. A woman of 65 was admitted to hospital in a semi-conscious condition. It was said that she had been in bed for a month prior to admission, complaining of general malaise, lassitude and extreme weakness. Mental disorientation had been present for the last two days and she had been difficult to rouse for the last twenty-four hours.

The patient's general condition was poor; temperature normal, pulse 80 per min. regular, and blood pressure 110/70. There was a petechial rash over the whole body, with a few ecchymoses on the extremities. The spleen was palpable about two fingers' breadth below the left costal margin, and the liver could just be felt below the right costal margin. No abnormalities were found in the cardio-vascular or respiratory system.

Investigations: Hæmoglobin 83 per cent. White cell count 4,200 per c.mm. (Neutrophils 3,200, Eosinophils 40, Monocytes 40, Lymphocytes 920). The red cells showed anisocytosis and poikilocytosis and some macrocytosis; a few nucleated red cells with orthochromatic cytoplasm and bizarre nuclei were seen. Platelet count 5,000 per c.mm. Bleeding time in excess of 35 minutes (Ivy), clotting time 5 minutes (Lee and White). Blood urea 60 mg. per cent. Lumbar puncture and cerebro-spinal fluid normal.

Bone marrow was obtained by sternal puncture and gave the following results:

	Per cent.		Per cent.
Myeloblasts	1	Lymphocytes	21
Premyelocytes	1	Plasma cells	3
Neutrophil myelocytes	6	Hæmocytoblasts	1
Young myelocytes	1	Basophil erythroblasts	4
Band myelocytes	6	Polychromatic erythroblasts	31
Segmented myelocytes	12	Normoblasts	12
Eosinophils	1	Leuco-erythrogenic ratio	1 : 1·09

An occasional megakaryocyte was seen.

Attempts to improve the patient's poor general condition failed; she grew steadily weaker and died on the eighth day after admission.

On post-mortem examination the spleen was found to weigh 535 g. and was uniformly enlarged. The surface was scattered with irregular white infarcts. The cut surface was firm and engorged to an almost black colour, with the white infarcts as previously noted. Test for free iron negative. The liver weighed 1175 g. Cut surface firm, with apparent swelling of the lobules. No discrete nodules were seen. On microscopy, however, small granulomata were seen to be scattered through the liver, spleen, kidneys and bone marrow. They were composed of reticulum cells with a somewhat faceted outline, and in a fair number there were typical Touton giant cells. There was no lymphocytic infiltration in the vast majority of them. One or two showed central necrosis or caseation. Scanty tubercle bacilli were seen in the spleen and liver. In the bone marrow the granulomata were fairly widespread, but no tubercle bacilli were seen. No tuberculous lesions were demonstrated elsewhere in the body.

Discussion

There are several points of similarity in these two cases. Both were admitted with a purpuric rash, low platelet count and prolonged bleeding time. In both the spleen was shown to be the site of active tuberculous infection; in the first case this was associated with an X-ray appearance of miliary tuberculosis of the lungs, and in the second case, with scattered tubercles in the liver, kidneys and bone marrow.

Since splenectomy appeared to effect a complete cure in case 1, it seems difficult to escape the conclusion that the thrombocytopenia was due to some disorder of splenic function, presumably brought about by the tuberculous infection—so-called "secondary hypersplenism." It has been suggested (Doan *et al.*, 1950) that there are three possible mechanisms by which an abnormally functioning spleen may affect the level of circulating blood cells:

1. Inherent or acquired vascular abnormalities with or without splenomegaly which permit large numbers of the circulating elements to "leak" into the parenchymal spaces. These spaces are provided with abundant cellular macrophage-scavengers ready to phagocytose particulate metabolic debris, to capture and destroy bacteria, and to engulf senile or prematurely damaged blood elements.

2. The circulating cells of the blood delivered from the bone marrow are defective, and the spleen withholds them from circulation.

3. The spleen may elaborate one or more inherent hormonal or acquired immuno-globulin antibodies, which may inhibit the maturation of the normal

cells of the blood in the bone marrow. Doan states that there is evidence to support all three of these possible mechanisms.

Whilst none of these three possibilities can be eliminated as the cause for the thrombocytopenia in our case 1, nevertheless we consider that the basic cause of the splenic dysfunction was due to the presence of tuberculosis in that organ. Thus it would be theoretically possible to treat the case from the outset on anti-tuberculous chemotherapy, were it not for the urgent need to correct the potentially dangerous prolongation of the bleeding time as soon as possible. In this case splenectomy was followed by a rapid rise in the platelet count and a restoration of the bleeding time to normal. On the other hand, treatment of active tuberculosis with appropriate chemotherapy causes at best a slow resolution of the lesions, and thus it is to be presumed that the application of such treatment to this type of case would scarcely lead to a prompt restoration of normal splenic function.

Case 2 was never fit to be submitted to surgery, and it would have been interesting to have observed the response to anti-tuberculous drugs in her case. Unfortunately the diagnosis remained obscure until post-mortem, when it required histological examination to reveal the granulomata in the liver, spleen, kidneys and bone marrow. We have only been able to find two previously reported cases in which thrombocytopenia was associated with evidence of tuberculosis in the marrow.

At the time these cases were seen the steroids were not freely available. The obvious danger of treating such cases with cortisone or ACTH is of a sudden disastrous spread of the tuberculous process. In this connection it should be pointed out that some cases diagnosed as " idiopathic thrombocytopenic purpura " may well be due to tuberculosis, and attempts at treating them with steroids may then lead to a spread.

It is conceivable that a combination of anti-tuberculous drugs and steroids would be a satisfactory treatment of purpura in tuberculosis.

Summary

Two cases of thrombocytopenic purpura in tuberculosis are reported. One patient died and post-mortem revealed acid-fast bacilli in the spleen and liver. A second case recovered after splenectomy.

We would like to thank Dr. Gordon, Dr. Marshall and Dr. Smith for the pathological investigations, and Dr. R. L. Mackay for permission to publish this report.

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IMPRESSIONS OF CHEMOTHERAPY IN THE OUT-PATIENT TREATMENT OF PULMONARY TUBERCULOSIS IN SINGAPORE

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Introduction

Remarkably little has been written about the effects of chemotherapy on patients with pulmonary tuberculosis in South-east Asia. Apart from a few isolated reports on the use of streptomycin during its earlier years, the literature in this part of the world contains only one work of any significance at all, and that is a report by Grove-White (1953) on the tuberculosis service in Singapore in the post-war years, with special reference to the Tuberculosis Treatment Allowance Scheme.

It was our original intention to collect together a very large number of out-patients in this clinic and to analyse them in order to draw conclusions about the effects of chemotherapy upon them. This proved to be much more difficult than we had anticipated. It was therefore decided to concentrate on cases who completed a course of streptomycin, given either by itself, or with INAH, or with PAS, or with INAH and PAS together, during the two-year period March 1952-May 1954. This particular period (*a*) was covered accurately by a clinic register of all cases completing a course of streptomycin; (*b*) represented a time during which the activities of the treatment centre were reaching (and were to maintain) a peak as regards numbers admitted; and finally (*c*) gave us an opportunity to follow up cases selected for further study from the later part of the period (May 1954) for approximately one year—that is to say until at least May 1955.

Following this plan, we discovered 780 cases in which the sputum was positive for acid-fast bacilli on at least one occasion, either on smear examination (approximately 98 per cent. were examined in this way) or on culture (perhaps 2 per cent. of the total), at some point or other during the two-year period. Of this total of positive cases, 461 (59·1 per cent.) were positive at the outset only; 27 (3·4 per cent.) were positive at the completion only; 277 (35·5 per cent.) were positive both at completion and outset; 14 (1·8 per cent.) were positive at the outset, but had no test recorded at the completion; 1 case appeared to have been positive at the completion but to have had no test recorded at the outset. Of those who had no test recorded at the completion it is certain that there were several who were quite unable to produce sputum, and the findings in the last case may be the result of an error in recording.

We hasten to point out that the figure of 780 in no way indicates the total

* Abridged.

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of cases, tuberculous or otherwise, which passed through the clinic during the period of study. It merely represents those cases who were known to have completed a course of streptomycin during that period and in whom at least one positive sputum result was obtained. It thus takes no account of the following classes of disease; (*a*) non-tuberculous chest conditions. (*b*) cases in which the diagnosis of pulmonary tuberculosis was established on the basis of combined clinical and radiological findings, and in which a positive result was not obtained during the period of study.

Category (*b*) includes a large number of unco-operative but nevertheless obviously ill patients who could not be persuaded to bring their sputum prior to the commencement of chemotherapy; a further group of young people with marked signs of toxicity and evidence of pleurisy with effusion, in whom chemotherapy was considered an urgent necessity; and finally a group in whom chemotherapy was started without bacteriological confirmation of tuberculosis because of a spreading infiltration after a period of two to three months' observation.

So great is the emphasis which is being laid nowadays on the need for bacteriological confirmation of tuberculosis before diagnosis or treatment that the existence of this category needs further clarification. The appearance of lack of proper procedure which it carries may be very real to workers in the comfortable and controlled atmosphere of a Western clinic, where beds are often available for treatment, and sometimes even for diagnosis, where laboratory facilities are unlimited, and where social services are such that really ill people are seldom required to work. Further East, these advantages are usually lacking. Until quite recently, the pressure of innumerable sick people with advanced disease has been such that accurate scientific procedure in dealing with tuberculosis has been well-nigh impossible. Our approximate figures would indicate that the total (780 positive cases) represents between 50 and 55 per cent. of the total of cases who received streptomycin during the period of study. This includes quite a large group on which the diagnosis was soon to be revised, or in which the disease was doubtfully active, but which were believed to warrant a chemotherapeutic trial.

From the total of 780 cases, 108 (13 per cent.) were eventually extracted for assessment of the effects of chemotherapy. This small number may in some measure be due to the strictness of the conditions which we applied, but these cannot account for it entirely, and it would seem to confirm our previous suspicion that chemotherapy in the treatment of pulmonary tuberculosis has its limitations in Singapore just as it does in other parts of the world. Any estimate of the effects of chemotherapy in the remaining 672 cases is futile; without exception they all required some additional therapeutic measure, or they resisted treatment or review to an extent which made further study impossible.

A striking feature of the work of this clinic from its earliest days has been the extensive use of the 4×5 inch photo-fluorograph, not only for diagnosis but also for all aspects of treatment. It was originally used as a diagnostic film only when the Association began its work of mass radiography in 1948, and it was the extraordinary number of cases of tuberculosis revealed radiologically by this campaign which forced the Association into opening a treatment centre, for Government facilities at that time were totally inadequate. In 1949, for

instance, the total number of tuberculosis beds available for a population of over 900,000 was approximately 450, with no separate hospital accommodation for old, destitute, and, incidentally, tuberculous patients. Even with the rapid increase in recent population, the proportion has not changed significantly, and it is still very difficult indeed to admit a patient for bed rest. If only for psychological reasons, it was at that time thought essential to do something for the large numbers of newly discovered cases who could not hope for institutional treatment. The treatment centre was therefore started in nearby premises. Clinical examinations were carried out by physicians, many of whom were volunteers. Blood sedimentation rate examinations were made, and sputum was examined by direct microscopy. The numbers of patients dealt with in the early days were enormous. In this colony streptomycin was first used in 1949, PAS in 1950, Thiosemicarbazone in 1951, and INAH in 1952. Prior to the introduction of these drugs, the treatment centre had to depend on the psychological but otherwise doubtful effect of calcium injections, together with general measures such as advice about sputum disposal, and the selection of nourishing food. The great majority of patients attending this Clinic are Chinese, with Hokkiens taking the lead, and Teochews and Cantonese sharing second place.

Following their main course of streptomycin, 190 cases (24·3 per cent.) received no further treatment, and were merely asked to return to the clinic for periodic radiographic and clinical check-up. Of these 190 cases only 108 have at present a follow-up period of one year or more since the cessation of chemotherapy, and the remaining 82 cases will not necessarily last the year without some form of new therapy being instituted. Further chemotherapy in some form or other was given to 130 cases (16·6 per cent.)—usually after a considerable interval. This may have been in the form of INAH or PAS alone, for the danger of early resistance associated with the use of a single drug was not appreciated at that time. Others, perhaps the majority over the two-year period, received INAH and PAS together. A few received a second course of streptomycin either given by itself or together with INAH or PAS. If this happened within the two-year period, then there is, of course, a possibility that their names appear twice in the register on two different occasions and under differing circumstances. Every effort has been made to detect and correct mistakes which might arise from this.

At the conclusion or very soon after the conclusion of the main course of chemotherapy, there were 439 cases (56·3 per cent.) on some form of collapse therapy; of these 77 cases (9·8 per cent.) were on AP treatment; 257 cases (32·9 per cent.) on PP treatment; and 33 cases (4·2 per cent.) who received both AP and PP sometimes simultaneously, and sometimes in close succession, as when an AP was unsuccessful, and PP was induced as the next best method of treatment. There were also 5 cases (less than 1 per cent.) which received AP treatment, and 30 cases (5·0 per cent.) which received PP treatment at the same time as some further form of chemotherapy. Finally, there were 28 cases (3·6 per cent.) which received either AP or PP, and which then defaulted or transferred to another hospital. In the latter cases, particularly if they went to the Government Tuberculosis Hospital, it is highly probable that the collapse measure would have been continued, as had been our intention. Total deaths

numbered 37 out of 780 (4·7 per cent.) of which 32 (4·1 per cent.) were known to have been certified with pulmonary tuberculosis as the primary cause of death.

In concluding this broad survey of the outcome following streptomycin in 780 sputum-positive cases of pulmonary tuberculosis, we would draw attention to two main points: (1) the number of cases (56·3 per cent. of the total) which required collapse measures either during or shortly after the main course of streptomycin in this period of study, and (2) the fact that 108 cases only (13·8 per cent. of the total) were found suitable for further study as to the effects of chemotherapy.

Close Analysis of 108 Cases

Basic Requirements

In selecting cases which might prove suitable for assessment of the effects of chemotherapy, we laid down certain basic requirements: (1) Tubercle bacilli must have been present in a recent smear and on at least one occasion. (2) All patients must be Chinese. (3) No treatment other than chemotherapy was to be allowed either during the period of chemotherapy or in the approximate one year following cessation. (4) The following cases were to be excluded: (*a*) Those who had received less than 60 grammes of streptomycin. (*b*) Those who had received a course of streptomycin alone without the addition of INAH or PAS. (*c*) Those in whom previous collapse measures or previous chemotherapy had been extensive, or markedly effective.

Methods of Treatment

In all 108 cases, streptomycin was given in a dosage of 1 gramme weekly, pure streptomycin sulphate being used in the vast majority. There were no cases of streptomycin sensitivity in the series; drug reaction of any kind has been very rare indeed with either streptomycin, INAH or PAS in this clinic. No case received less than 60 grammes, and the highest total was 180 grammes. The cases may be grouped as follows:

Group 1:	60- 90 g.	of streptomycin:	19 cases.
Group 2:	91-120 g.	„	30 „
Group 3:	121-150 g.	„	36 „
Group 4:	151-180 g.	„	23 „

From this it can be seen that the majority received between 91 and 150 grammes, a figure that still holds true for the majority of cases at this clinic. In the absence of more definite guidance from other centres of study we have pursued the policy of continuing chemotherapy until at least six to eight months after the maximal clinical and radiological improvement, a policy which implies a streptomycin total for the average case of approximately 120 grammes, requiring sixty weeks of treatment. In this series, the duration of treatment has varied between eight months and two years, some of the longer periods occurring in patients whose two-monthly photo-fluorographs showed little evidence of improvement even after a comparatively high total of streptomycin. Other factors have occasionally prompted us to continue chemotherapy to an unusually high total.

The principle of treating as out-patients very large numbers of people suffer-

ing from an infectious and debilitating condition was adopted in this clinic five years ago, as otherwise the numbers treated would have been so small as to render our work almost useless. The intermittent use of streptomycin, combined with either INAH or PAS, was originally used here because it was thought to be an efficient method of treatment. At the present time there appears to be a great difference of opinion as to the optimum régime to follow; in having to choose between the views such as those expressed by the Medical Research Council in Britain on the one hand, and the Veterans Administration in America on the other, we have felt justified in following the latter trends, and in continuing the intermittent use of streptomycin, combined with either INAH or PAS. There are numbers of local factors which greatly favour this routine and amongst these is the deep, almost religious, faith which the Chinese have in the power of the injection, and their natural aversion on the other hand to swallowing large quantities of tablets by mouth. We have lost patients both by refusing to give injections of various kinds when the diagnosis was in doubt, and also by insisting on a reasonable dosage of PAS despite the patients' complaints. The injection has, in some cases, become a device by which one can establish the patient's confidence and link him securely to the clinic so that he will continue to attend for investigation and the proper treatment. In this way, it has sometimes been possible to prove that he is tuberculous, or, which is equally important, that he is not. Possibly the strongest objection to the routine use of combined INAH and PAS lies in the suspicion that the tablets are not taken by the patient although they may be collected regularly from the dispensary. We do not insist on the larger doses which have been recommended, and it is the routine to give only 10 grammes PAS daily for male, and 8 grammes daily for female patients. Daily attendances for streptomycin is not practical for patients, some of whom live as far as eight miles from the clinic, or for those who continue working while receiving treatment, and who sometimes find difficulty in attending for a mere two injections per week.

Over 90 per cent. of the cases in this series attended the clinic for their treatment; a few who were extremely ill at the outset were visited by our home nurse and received a short period of treatment while they were resting in their homes. Overcrowding amongst the poorer classes is frequently appalling. In reply to the question "Where do you live?" it is not uncommon to hear a patient reply: "I live in number 5"—and he is referring, not to the number of his house, but to the number on his bunk in the room where he rents living space. We have sometimes felt that greater rest is to be found by the patient making the journey to the clinic where he can at least doze for an hour or two in the comparative peace of our waiting rooms.

The age range of our cases was 17-36, of whom 72 were male and 36 female.

Occupation

This is reported as it was recorded at the outset on the patient's own evidence; from the total of 108, 4 claimed to have no occupation at all; 42 were in light occupations; 17 were in moderately heavy occupations; 18 were in heavy manual work, and the remaining 27 were housewives, many of whom had five or more children besides a husband to look after and who were prob-

ably, therefore, working as hard as anybody in the series. Four women were working as washerwomen, one as a labourer, and the remainder were in light occupations.

Of the 72 men, the majority (39) were in light occupations, of which shop assistants were the most common. In the entire series there were only 6 patients in the educated class; these comprised 2 druggists, 1 factory supervisor, 1 compositor, 1 draughtsman and 1 teacher.

Possibly the most interesting of all were the men engaged in heavy work, for a number of these continued their occupation while attending the clinic for treatment. The group included 13 patients: 3 carpenters, 2 trishaw riders, and 8 others doing various types of heavy building and labouring work.

The policy of allowing patients to work at heavy occupations while they are suffering from tuberculosis of the lungs has been possible owing to the Chinese ability to carry on heavy work while suffering from moderately or even far-advanced pulmonary tuberculosis.

Bacteriology

Laboratory facilities for dealing with laryngeal swabs, for sensitivity tests, and for culture work generally, were not introduced into the clinic until 1954, and prior to this these examinations were performed for us by the local general hospital. Results from these methods of examinations do not figure to any extent in this report. All 108 cases had at least one positive result for acid-fast bacilli recorded on smear examination by direct microscopy at the outset of their treatment. We took careful note of the results of smear examination at the termination of treatment, and also at a point approximately one year later. The lack of significance in the recording of a single negative smear is well understood, and we certainly would not attach much importance to it. The recording of a single positive result is more important than the recording of several negative ones.

Sputum smear results are shown in Table I, as set out against the initial radiological extent of disease and the initial presence or absence of cavitation.

TABLE I.—SPUTUM SMEAR FINDINGS AS SET OUT AGAINST THE OUTSET RADIOLOGICAL EXTENT OF DISEASE AND THE OUTSET PRESENCE OR ABSENCE OF CAVITATION

One case, marked *, was positive on culture

Radiological extent of disease at outset	*On completion*	*Chemotherapy*	*One year later*	
	Positive	*Negative*	*Positive*	*Negative*
Minimal 33 cases	1	32	1	32
Mod. adv. 50 cases	4	46	6	44
Far. adv. 25 cases	9	16	7 and 1*	17
Cavitation at outset absent or doubtful 68 cases	3	65	4	64
Cavitation at outset definitely present 40 cases	11	29	11	29

Radiological Extent of Disease

The rules laid down by the N.T.A. in their 1950 booklet on Diagnostic Standards have been followed closely, except where it seemed too rigid to describe the true state of affairs. At least one case, for instance, improved considerably but did not technically qualify for removal from " far-advanced " to " moderately advanced " grade, and in such cases we have recorded " radiological condition improved."

The basic requirements which we imposed on the selection of cases rob the initial figures of significance. It should not be assumed, for instance, that the majority of cases admitted to the Clinic during the period of study were suffering from moderately advanced disease, though it so happens that this may well be true.

TABLE II.—RADIOLOGICAL CONDITION (*a*) AT COMPLETION OF CHEMOTHERAPY, AND (*b*) AT A POINT APPROXIMATELY ONE YEAR LATER, AS SET OUT AGAINST THE INITIAL RADIOLOGICAL EXTENT OF DISEASE

	On completion of chemotherapy			*One year later*		
Radiological extent of disease at outset	*No change*	*Improved*	*Deteriorated*	*No change*	*Improved*	*Deteriorated*
Minimal 33 cases ..	3	30	0	32	0	1
Mod. adv. 50 cases ..	4	44	2	46	1	3
Far. adv. 25 cases ..	1	21	3	18	1	6

Cavitation

We classified this as simply as possible into the three categories: " absent," " single, " or " multiple," When cavitation was doubtful we wrote " absent," and there may therefore be a tendency to under-statement in this respect. Over-reading of small films, however, is an almost classical error (Zacks, 1949) and occurs much more frequently, particularly with inexperienced readers, than under-reading. We made no attempt to record the size of the cavities and the changes in their size, since it seemed unlikely that detailed measurements would yield relevant information. Close estimations on 4×5 inch photofluorographs are in any case open to criticism; there is some exaggeration of cavity size, especially in those located posteriorly, and at the time of writing we are not sure what allowance should be made for this. At the outset of treatment, cavitation was absent in 68 cases (62·9 per cent.), single in 27 cases (25 per cent.), and multiple in 13 cases (12 per cent.). At the completion of treatment, it was absent in 90 (83·3 per cent.), single in 11 (10 per cent.), and multiple in 7 (6·5 per cent.). Expressing this somewhat differently, Table III shows the fate of the 40 cases in whom cavitation (single or multiple) was present at the outset of treatment.

Clinical State, including Symptomatology, Weight Changes, and the Incidence of Hæmoptysis

It has been difficult to note with accuracy the changes in a patient's clinical state at the various stages of this study. We made an attempt to correlate the

TABLE III.—CAVITY STATE IN 40 CASES (*a*) AT COMPLETION OF TREATMENT, AND (*b*) AT A POINT ONE YEAR LATER AS SET OUT AGAINST THE PRESENCE OF SINGLE OR MULTIPLE CAVITATION AT THE OUTSET

Cavity state	*At completion of chemotherapy*			*One year later*		
	Single	*Closed*	*Multiple*	*Single*	*Closed*	*Multiple*
Single cavitation definitely present 27 cases	9	18	0	16	11	0
Multiple cavitation definitely present 13 cases	2	5	6	2	5	6

notes which had been made about appearance, sense of well-being and symptoms generally. A very broad statement on these lines shows that 95 cases (87·9 per cent.) were better at the completion of treatment, while 12 (11·1 per cent.) were the same, and one case had died. A year later, 79 cases (73·1 per cent.) were in more or less the same clinical state as at completion of treatment; 10 cases (9·2 per cent.), however, were worse, and 19 cases (17·6 per cent.) had improved somewhat without any treatment at all during the one year of observation.

Having tried to make this assessment, we now realize that it is an unprofitable item to include in an objective study: there is a tendency to make the assessment on the records of weight gain, sputum results and ESR, and possibly the most that this can hope to do is to guard the patient from the misleading comment, " radiologically improved," when in fact he is deteriorating rapidly from heart failure and carcinoma of the bowel.

In constructing Table IV, we have regarded an increase of 5 lb. (2·25 kg.) as significant, and the term " better " in the table therefore indicates a gain of at least this amount and often more. Weight loss is a frequent presenting symptom of pulmonary tuberculosis in this area, and weight gain, on the other hand, with out-patient chemotherapy, is sometimes very striking. Thus in the series of 108 we had four patients who gained respectively 30 lb. (13·5 kg.), 24 lb. (10·8 kg.), 23 lb. (10·3 kg.), and 21 lb. (9·4 kg.), and there were many others who gained more than a stone on chemotherapy.

TABLE IV.—WEIGHT CHANGES (*a*) AT COMPLETION OF TREATMENT, AND (*b*) AT A POINT ONE YEAR LATER, AS SET OUT AGAINST THE OUTSET RADIOLOGICAL EXTENT OF DISEASE, AND THE OUTSET ABSENCE OR PRESENCE OF CAVITATION

Radiological extent of disease at outset (A) *and the presence or absence of definite cavitation at outset* (B)	*Completion of treatment*			*One year later*		
	Same	*Improved*	*Worse*	*Same*	*Improved*	*Worse*
(A) Minimal, 33 cases	8	25	0	17	13	3
Mod. adv., 50 cases ..	14	33	3	26	13	11
Far adv., 25 cases	5	19	1	19	2	4
(B) Cavitation absent or doubtful, 68 cases	17	49	2	38	20	10
Cavitation definitely present, 40 cases	10	28	2	21	8	11

In the term "hæmoptysis" we have included any definite statement of blood staining in the sputum. Fifty-four cases (50 per cent.) had hæmoptysis recorded at some point or other during the period of study. Table V shows the incidence as contrasted with the radiological extent of disease at the outset, and also with the absence or presence of definite cavitation at the outset.

TABLE V.—HÆMOPTYSIS

Radiological extent of disease at outset (A) *and the presence or absence of cavitation at the outset* (B)	*At outset*	*Subsequently*	*Both at outset and subsequently*
(A) Minimal, 33 cases	13	4	2
Mod. adv., 50 cases	19	5	4
Far adv., 25 cases	9	4	1
(B) Cavitation absent or doubtful, 68 cases ..	26	7	3
Cavitation definitely present, 40 cases ..	15	6	4

Erythrocyte Sedimentation Rate

This test has been performed on all new patients who would consent to it, and on over 90 per cent. of established treatment centre cases. It has never been popular with the patients who view it as a sinister weakening of their reserves of blood. There are so many conditions in this part of the world which may affect this examination—anæmia, parasite infestations, and oral sepsis, to mention only a few. Among those in whom a raised reading has been useful, however, are those whose reading remained high despite apparent quiescence of a lung lesion, thus stimulating us to look for some other, co-existent disease.

Table VI shows the ESR readings in the 108 cases in this series. All estimations were made by the Westergren method.

TABLE VI.—ERYTHROCYTE SEDIMENTATION RATE
(mm. in the first hour: Westergren)

Radiological extent of disease at outset (A) *and the presence or absence of cavitation at the outset* (B)	*At outset*			*At completion of treatment*		
	12 or less	*13 to 30*	*31 or more*	*12 or less*	*13 to 30*	*31 or more*
(A) Minimal, 33 cases	9	11	13	24	8	1
Mod. adv. 50 cases	5	14	31	29	17	6
Far adv., 25 cases	0	1	24	10	7	8
(B) Cavitation absent or doubtful, 68 cases	12	18	38	42	22	4
Cavitation definitely present, 40 cases	2	8	30	21	10	9

Other Diseases Present Including Opium Addiction

From the 108 cases, other conditions and diseases were as follows:

Diabetes	2 cases
Bronchial asthma	3 cases
Mitral stenosis	1 case
Hypertension	1 case
Pyelitis (non-T.B.)	1 case

Of more definitely tuberculous origin, there were 6 patients (5·5 per cent.) who were recorded as having tuberculous laryngitis, and one other patient who had a spontaneous pneumothorax. Opium addicts on their own confession numbered only 2, but there were at least 4 others who looked extremely like addicts and yet denied it. " Opium lung " is apparently a well-known pathological entity in the post-mortem rooms of Singapore, but we can find no literature on it at the time of writing, and no good references to typical radiographic changes. The debility of opium addiction is often so profound that one might reasonably suppose opium addicts (*a*) to contract tuberculosis more easily, and (*b*) to show a poor resistance to the established disease. There is no evidence to show that the first supposition is true, and there are indeed many Chinese in Singapore who believe that a moderate amount of opium preserves the body (and the mind) into old age. As to the reaction of the addicted host to his disease, it is our belief that the majority of opium addicts with phthisis show a curiously slow-moving type of disease with a marked tendency towards fibrosis.

Previous and Subsequent Anti-Tuberculosis Treatment

We do not believe that such treatment can have influenced any broad conclusion about the effects of their subsequent and main course of streptomycin combined with either INAH or PAS. There were, for instance, 3 cases who received less than 30 grammes of streptomycin (alone), and 3 others in whom the collapse measure was maintained for less than 5 months, being abandoned because the collapse was unsatisfactory. One further AP case developed effusion during treatment, required aspiration, and entered the period of study with a markedly thickened pleura, and active disease underlying it. There were, on the other hand, 6 cases in whom AP or PP had been effective for a least one year, and whose disease may therefore have been considerably influenced prior to the main course of streptomycin.

Subsequent treatment has so far been required by 5 cases (4·6 per cent. of the total 108). All of them have received further chemotherapy—usually INAH and PAS—and there have been no subsequent AP or PP inductions.

Discussion

From the total of 780 cases reviewed broadly in the first part of this paper, the figure of 439 (56·3 per cent.) who required reversible collapse measures either during or shortly after the main course of chemotherapy may seem remarkably high. The majority were PP cases in whom the collapse was induced as a kind of holding measure in cases whose disease had the radiological and clinical appearance of instability, but for whom no other form of treatment was suitable. They continue to form the bulk of our collapse cases, and there

has been no significant reduction in the proportion of PP cases in the clinic during the last year or so. During the period of study it was probably true to say that the proportion of AP cases was considerably higher than in the other centres, and also significantly higher than our present-day figures. This was due to a number of different factors: (1) it was our policy at that time to induce an AP in certain cases without definite evidence of cavitation. This now happens very rarely. (2) Surgical facilities were seriously lacking; there was, and still is, no organised thoracic unit in the Colony. (3) The tremendous advantages of chemotherapeutic drugs had brought a large number of cases to a stage which they could never have otherwise hoped to reach—namely that at which a collapse measure could be considered. This is perhaps one of the main reasons why our refill clinics still flourish, and the numbers dealt with each day have frequently astonished overseas visitors. AP and also PP inductions have been performed routinely on out-patients since the early days of the clinic. No pre-medication is given. Up to 250 ml. are given for AP, and up to 700 ml. for PP induction, and following this the patient is required to rest for a minimum of one and a half hours. It is often difficult to convince the Chinese patient that this is necessary. The majority return home by bus; a few by taxi or car. We have encountered one returning on a bicycle. They are advised to stop work for at least one day, but this advice is not always taken. It is exceptionally rare for any untoward effects to manifest themselves as a result of this routine. The lack of surgical facilities due to lack of money and not to Government indifference has had a very great influence on programmes of treatment.

There is, however, now a greater tendency for us to refer for resection cases in whom we might previously have attempted an AP, but there is no organised thoracic unit, and cases are nursed in the wards of the Government tuberculosis hospital, and operated upon in the general surgical wards of the Government General Hospital. The present refusal rate from all ethnic groups is extremely high and we shall therefore continue the wide-scale out-patient treatment of pulmonary tuberculosis in this Clinic.

A broad clinical assessment shows that 95 out of 108 (87·9 per cent.) were better at completion of treatment and that there was little down-grading after one year.

The high incidence of hæmoptysis (54 cases, *i.e.* 50 per cent.) recorded at some point or other during the period of study may in part be due to the fact that we have included under this heading all cases in whom blood staining of any amount was noted. It also supports our clinical impression that hæmoptysis is a frequent sign of tuberculosis amongst the Chinese in Singapore, and that it should be regarded as very strong presumptive evidence of tuberculosis until proved otherwise.

A unique feature of the management of these 780 cases has been the extensive use of the 4×5 inch photo-fluorograph, not only for the initial diagnosis (combined with bacteriological and clinical findings), but also for the initiation and control of treatment. Sir Harry Wunderley described the 4×5 inch films from this Clinic as being the best which he had seen in Australia. Small detail is still extremely well preserved in this bad climate after four or five years on most of these films; some of those used for reproduction in this report are more than two years old, and have lost little if any detail. We contend that its wider use should be seriously considered.

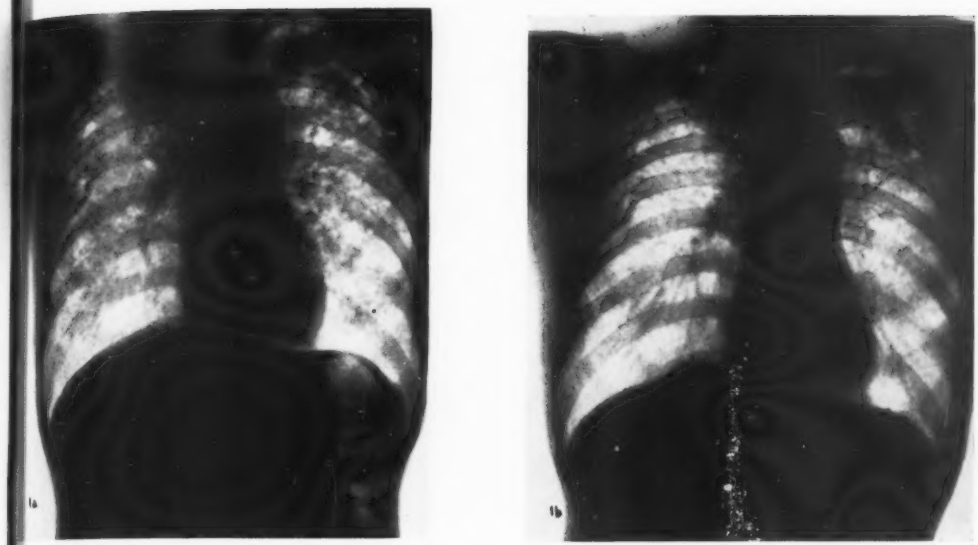


FIG. 1.—Male aged 55 years. Former trishaw rider. Opium addict. FIG. 1a at outset; FIG. 1b taken 14 months after cessation of chemotherapy. Lived three miles from the Clinic and attended bi-weekly for streptomycin to 105 grams, together with daily INAH. Unable to work at outset because cough, dyspnœa and general weakness. Considerable clinical and radiological improvement, but unable to return to former work. Old empyema drainage wound at angle of right scapula.

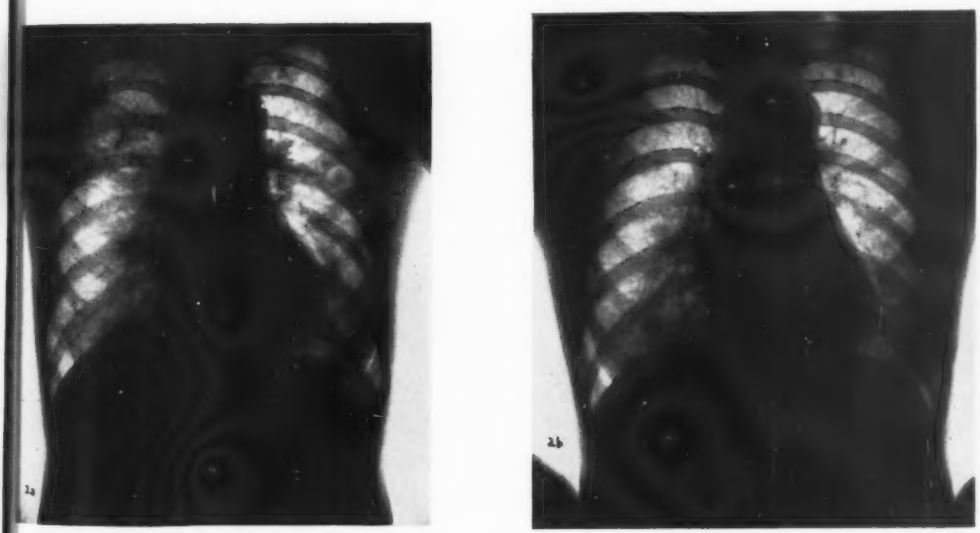


FIG. 2.—Female Cantonese aged 44 years. Housewife. Four children. FIG. 2a at outset; FIG. 2b taken one year after cessation of chemotherapy. Attended bi-weekly for streptomycin to 120 grams together with daily INAH. Apparently complete resolution of infiltration in the right upper and middle zones, and of infiltration in the left middle zone. Maintained heavy household duties throughout period of treatment.

To face p. 254

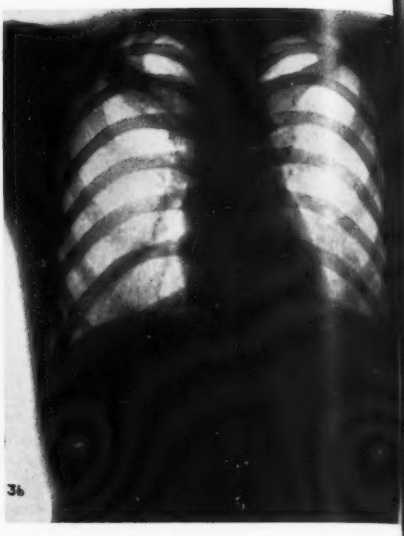
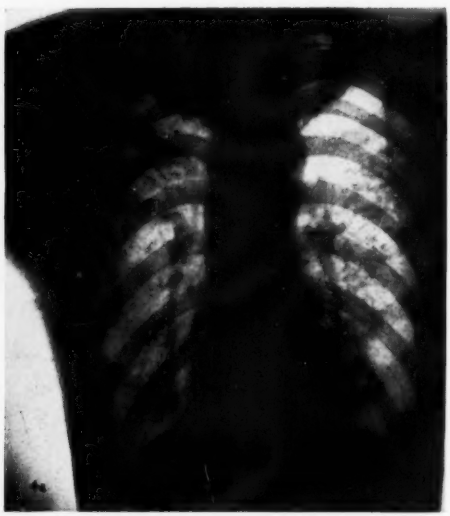


FIG. 3.—Female Hokkien seamstress aged 19 years. FIG. 3a at outset; FIG. 3b taken 9 months after cessation of chemo-therapy. Lived four miles from the Clinic and attended bi-weekly for streptomycin to 165 grams, together with daily PAS. Considerable resolution of lesions throughout both lungs. Returned to full work half way through course of treatment.



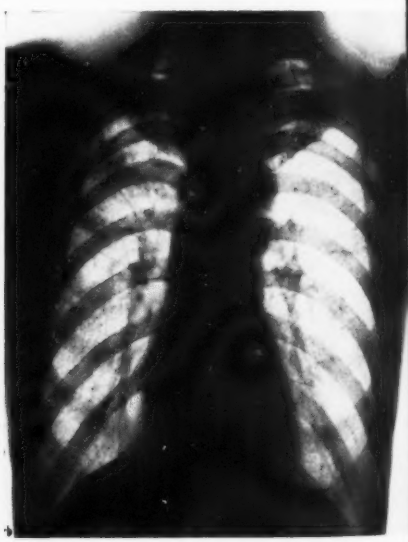


FIG. 4.—Male Cantonese painter aged 49 years. FIG. 4a at outset; FIG. 4b taken one year after cessation of chemo-therapy. Lived eight miles from the Clinic, and attended bi-weekly for streptomycin to 150 grams, together with daily PAS. Cavity closure on the right, and considerable resolution of lesions throughout both lungs generally. Returned to work against advice a few months before stopping chemotherapy; later took up heavy building labour, and developed a left spontaneous pneumothorax.

Besides the initial report by the radiologist in this clinic, all films are invariably seen by at least one other physician before any news is communicated to the patient.

Summary

780 sputum-positive cases of pulmonary tuberculosis are described with regard to their broad outcome following a course of streptomycin, combined with either INAH or PAS. All cases completed a course of streptomycin between March 1952 and May 1954. With the exception of a very few cases who received some of their earlier treatment at home, all 780 cases attended the clinic for out-patient treatment.

Attention is drawn to the number of cases who eventually required some form of collapse treatment (56·3 per cent) and to the fact that only 108 cases (13·8 per cent.) could eventually be extracted for some assessment of the effects of chemotherapy.

In these 108 cases, the results of chemotherapy are described. The view is expressed that out-patient chemotherapy is remarkably successful in the treatment of pulmonary tuberculosis in the Chinese of this Colony, and that it is fully justified as one method of attack on the existing problem.

Emphasis is given to the way in which the 4×5 inch photo-fluorograph has been used extensively not only for diagnosis but also for the institution and control of treatment in pulmonary tuberculosis. The belief is expressed that this film has been outstandingly efficient during the five years of its use in this way. A plea is made for its wider application and trial in tuberculosis work.

We are greatly indebted to the Director of the Royal Singapore Tuberculosis Clinic for permission to publish this article, to Sir Harry Wunderley for permission to quote from a personal communication, and to Dr. Owen Clarke for much useful information and advice.

The views expressed in this article are those of the authors, and not necessarily those of the Royal Singapore Tuberculosis Clinic, or of the Singapore Anti-Tuberculosis Association.

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DOMICILIARY TREATMENT OF PULMONARY TUBERCULOSIS

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From the Tuberculosis Clinic, Dunfermline

The acute shortage of beds in sanatoria after the last war gave rise to concern that a patient's disease might advance to such an extent as to diminish or interfere seriously with the chances of recovery. Efforts had to be made to institute some form of domiciliary treatment, more especially in view of the ever-increasing numbers awaiting hospital admission. Various schemes for the induction of artificial pneumothorax or pneumoperitoneum, either at home or in hospital, were devised; the collapse measures once instituted were satisfactorily maintained from the home, so that patients were actually recovering from pulmonary tuberculosis without prolonged sanatorium treatment.

Toussaint (1952) gave an indication of what could be achieved by domiciliary treatment combined with the use of hospital beds. He made fairly extensive use of collapse therapy, using both artificial pneumothorax and pneumoperitoneum; these measures were instituted in hospital and, within a few weeks, the patients were discharged home for continued treatment, the chest physician attending the patients' homes to give refills. Stradling (1951, 1955) has also described the short-term use of hospital beds to institute collapse measures which were also maintained from the home. Both these authors have shown that it was possible to conduct a home therapy programme with considerable success; as Stradling has remarked on reviewing a series of patients who had received a major part of their treatment outside sanatorium, they "fared no worse than is usual for sanatorium-treated patients."

With the advent of antibiotics, the outlook for the tuberculous patient has been completely altered; increasing numbers of patients have been successfully treated at home by antibiotics alone, with the result that we now find many sanatorium beds are becoming vacant, both in this country and the U.S.A. Chest physicians have been able to start all recently diagnosed patients on antibiotics at home; by the time the usual three or four months' waiting period for a hospital bed had elapsed, many of those patients had made such striking progress that hospitalisation was no longer considered necessary. Indeed, Deuschle *et al.* (1954) and Robins *et al.* (1954) have shown that the decisive element in the unhospitalised tuberculous patient is chemotherapy.

However, the use of antibiotics means that certain other aspects of domiciliary treatment must be considered. These are:

(*a*) Suitable home conditions.
(*b*) Co-operation from the patient.
(*c*) Adequate supervision by the chest physician.

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Suitable Home Conditions. At the very minimum, this would imply that the patient should have his or her own room with some reasonable standard of comfort and with the attendance of a relative, while the patient is confined to bed, to provide meals and simple nursing requirements. Most relatives are only too anxious to lend a willing hand. A surprising standard of comfort can be obtained even in the poorest homes, and it is the exception in this essentially mining area to find a home where conditions are such as to make domiciliary treatment completely inadvisable. Exceptions there are, of course, but it is precisely those homes with gross overcrowding, little comfort and a low standard of living that would rule out domiciliary treatment, more especially when it is considered that prolonged bed rest must feature very largely in the treatment of many patients.

The presence of children in the household does not preclude home treatment, provided reasonable isolation of the patient can be secured. Those children are seen as contacts and, where necessary, given BCG. It is not considered essential to isolate any child requiring BCG. In any case, the spread of infection to a child has usually occurred before the source of infection has been diagnosed and started on treatment. Once the patient has been diagnosed, instructed about the disposal of the sputum and started on antibiotics, the danger period for the spread of infection has usually passed.

Co-operation from the Patient. Patients are invariably willing to accept advice. It should be emphasised that in the poorest of homes patients can be most co-operative. It is frequently found that patients refuse to leave the family circle to go into hospital, more especially if antibiotics have been started at home.

From the psychological aspect, the patient at home appears a more contented individual than the one in hospital, for he is no longer isolated from his home surroundings nor has he to make the adjustments demanded of a sanatorium life. Even although it is considered that the discipline of hospital life is important in guiding the patient to recovery, it can be maintained that with proper supervision this training can be given at home.

The elderly patient, especially, should be kept in his home surroundings whenever possible; little is to be gained from admitting him to an institution merely to have chemotherapy, for so few of those elderly patients can ever hope for any alternative treatment. Unless it be to isolate a patient with active disease from an overcrowded and unsuitable home, what is to be gained by admitting him to hospital !

Another class of patient who is much better looked after at home from the outset is the psychological misfit, the patient who takes his discharge from hospital against medical advice or is discharged for disciplinary reasons (the irregular discharge). American authors (Tedesco, 1953, and Lorenz *et al.*, 1955) have attempted to analyse the causative factors leading to those irregular discharges; absence from home with its attendant difficulties was a predominant feature in a large proportion of the patients investigated; " in the overwhelming majority of irregular discharged cases, the departure from the hospital can be attributed to either factors arising within the patient or in the patient's home situation " (Tedesco). Lorenz *et al.* viewed the problem from another angle—namely, that of the unskilled, lower income groups who

had difficulty in adjusting to the prolonged hospitalisation. Despite the fact that these inadequate personalities leave hospital on one pretext or another, many will continue to attend a clinic and accept antibiotic treatment. This treatment is not necessarily an end in itself but, if sufficient improvement takes place to make surgery a possibility, these patients are more likely to settle in hospital.

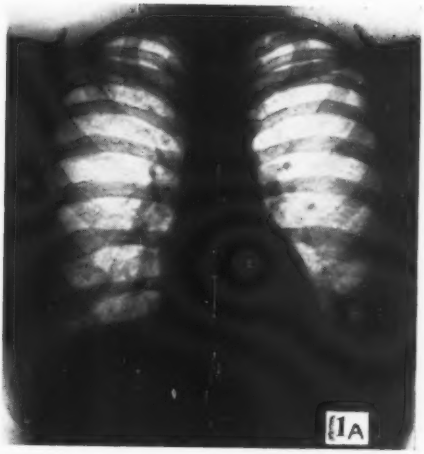
Illustrative Cases

All stages of pulmonary tuberculosis have been supervised at home. Minimal lesions have rarely been admitted to hospital and the few admissions were necessitated by unsuitable home conditions. Even moderately advanced patients have responded satisfactorily at home, as can be seen in Fig. 1; the lesions seen were actually cavitated on tomogram. Fig. 2 is of interest in that this woman broke down two years after leaving a sanatorium with well-calcified disease; her deterioration occurred as a result of psychological stress when she found she was no longer considered employable by a number of different employers. She had treatment at home, with a satisfactory result. Some far advanced patients have also been treated successfully at home. Figs. 3 and 4 show two such patients. The patient in Fig. 3 lived by herself in a good home and was entirely dependent on neighbours for her main meals; she refused to go into hospital, as both her husband and daughter at that time were having prolonged hospitalisation. Fig. 4 illustrates the improvement that might be expected in an old man whose home circumstances were not of the best but who responded satisfactorily in his own environment.

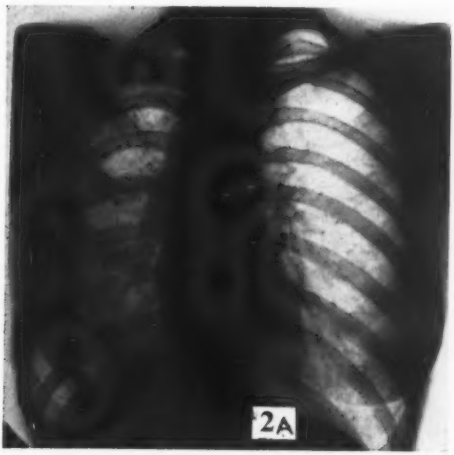
All the patients in this survey had routine bed rest; this was well maintained in the moderately and far advanced cases, and there was a surprising degree of co-operation in accepting the strict bed rest from the outset.

However, Mitchell and Knudson (1950) have observed that the type and duration of bed rest in pulmonary tuberculosis is still in great need of clarification. They wondered how much strict bed rest differed from the less stringent regimen of modified bed rest. They posed a further question—" Is it more important that the patient remain within the confines of a bed or that he spend most of his time in a relaxed and, more particularly, horizontal position? Does the type or the duration of bed rest play the more important part in the healing of pulmonary tuberculosis?" These observations were made in the pre-antibiotic period, but Mitchell (1954) has again emphasised the need for bed rest under sanatorium conditions. While the patients in this review would appear to have co-operated in observing the prescribed bed rest, there was obviously no control over their activities throughout the day. Nevertheless, such bed rest as may have been observed in most of the patients under domiciliary treatment has been adequate in all cases to ensure that no deterioration has so far occurred. It is admitted that no long-term follow-up is possible at this stage, but with satisfactory radiological improvement in all cases and with the sputum T.B. negative, it is possible to anticipate that there will be no more patients showing deterioration than there would have been under sanatorium conditions.

It might even be possible to modify considerably our attitude to bed rest and even to do without it altogether in the patient with a minimal lesion.



Female, age 28. Sputum T.B.O. Refused to leave her children to go into hospital. Streptomycin given 1 g. three times a week with P.A.S. Total streptomycin 42 g. Then P.A.S. and isoniazid for two months. Chemotherapy stopped when P.A.S. upset patient. Total bed rest six months.



Female, age 27. Sputum T.B.+ Total streptomycin 96 g. with P.A.S. and isoniazid 200 mg. Chemotherapy was stopped when the patient developed thyroid enlargement. As tomograms thereafter showed no definite cavity, chemotherapy was not resumed. Total bed rest ten months.

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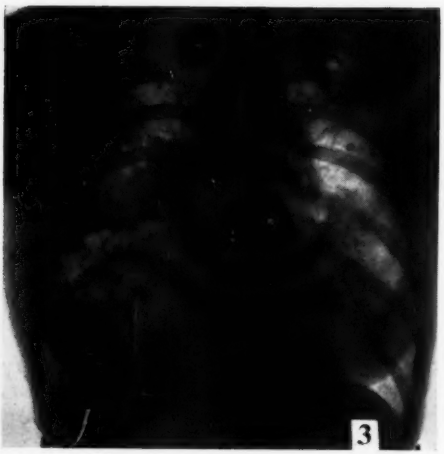
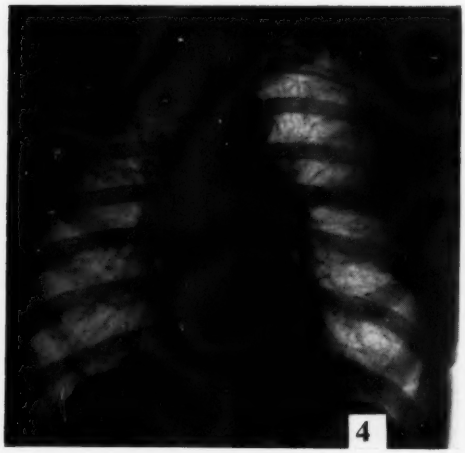


Female, age 59. Sputum T.B.+ X-ray deterioration three years after original plate. P.A.S. and isoniazid 300 mg. daily for eight months, then switched to streptomycin with P.A.S. Total streptomycin 64 g. P.A.S. and isoniazid have been continued during the past year. Bed rest for six months. She got up on the return of her daughter from hospital.



Male, age 67. Sputum T.B.+ Refused to go into hospital. Total streptomycin 112 g. with P.A.S. and isoniazid 200 mg. daily. P.A.S. and isoniazid have been continued for three months. Bed rest for six months, but doubtful if this was rigidly adhered to.

Both Mitchell (1954) and Dressler *et al.* (1954) have suggested that this might be possible under hospital conditions. From personal experience of domiciliary treatment during the past two years it is considered that the minimal lesion can be treated by modified bed rest. Indeed, when the results of mass radiography are reviewed, it is surprising to find that large numbers of the general public have apparently healed their disease without the need for any bed rest whatsoever. Would it not be possible then to allow the patient with minimal disease to be ambulant from the outset and to control his disease by suitable antibiotics? A start has been made in treating patients along these lines in this clinic, but it is not possible to present any results at this stage.

The Use of Antibiotics

In this survey, streptomycin was given 1 g. three times per week with PAS in the original cases; now it is given 1 g. daily over a prolonged period, the total streptomycin amounting to 150 to 200 g.; thereafter, the patients have continued chemotherapy with isoniazid 200/250 mg. daily in combination with PAS. The use of prolonged chemotherapy is considered important, several patients have now had chemotherapy for two years, particularly where the disease was moderately or far advanced. Long continued treatment would appear to be the key to success, whether the patient is at home or in hospital. Dooneief and Hite (1954) even remark that the time has come to explore very prolonged, perhaps lifelong, treatment with anti-microbial agents in some patients. Their remarks refer in particular to patients who have had hospital treatment with surgery; they were allowed to return home and resume gradually full activities with continued drug therapy.

Several unco-operative patients (the irregular discharge group) have been treated with a combination of PAS and isoniazid. Some have become sputum negative and remained so, even on returning to work against medical advice. Others are still sputum positive, but with the bacterial content of their sputum considerably reduced. From the point of view of infectivity, it is important to use every means at our disposal to try to sterilise the sputum of those patients. Chemotherapy is treatment which they readily accept.

The good " chronic " poses much the same problem; unfortunately, in many cases this patient has had advanced disease before antibiotics became generally available, and he has probably had frequent inadequate courses of chemotherapy during recent years, with its attendant risks of developing resistance. It might still be worth while to give them the benefit of long continued chemotherapy, even as ambulatory patients, using isoniazid and PAS, more especially in view of recent work with isoniazid. American authors, indeed, have suggested that isoniazid might be used by itself, despite the apparent difficulties this might create in developing isoniazid-resistant organisms. In this country Fox and Sutherland (1955) have shown that the possible clinical disadvantages due directly to the development of isoniazid resistance is inconclusive. Nevertheless, at this state of our knowledge of antibiotics it would not be deemed advisable to prescribe anything other than a combination of drugs.

Many patients after treatment at home will still be found to have persistent

disease requiring admission to hospital for collapse therapy or some form of surgery. The very success of antibiotics in making surgery available has, in itself, posed the question of the ultimate need for surgery in many patients. Doubts arise about the need for segmental resections and lobectomies in the sputum-negative patient when resected specimens in many cases fail to reveal active disease. With such patients it is probable that long continued chemotherapy would eventually successfully sterilise their lung lesion, even although it has been shown by Hobby (1955) that tubercle bacilli could still be isolated from resected specimens after prolonged chemotherapy, using appropriate cultural techniques; but it should be emphasised that none of the patients in that report received more than twelve months of chemotherapy, nor did they receive streptomycin on a daily basis. It has also been shown by Mitchell (1954) that any interruption of treatment had a seemingly unfavourable relationship to results. This was true of the extent of disease and of the pre-treatment drug status, and decisively so in the original treatment group. These findings make the need for further elucidation of these problems in chemotherapy most important, but these are problems which will face the patient whether he is at home or in hospital. The very fact that a patient is at home is bound to delay surgery; several patients were considered in need of surgical treatment and antibiotics were continued at home to that end. However, with this necessarily prolonged chemotherapy they were found to have made such progress that surgery was no longer considered necessary.

It must be recognised that the treatment of pulmonary tuberculosis has been completely revolutionised by the introduction of antibiotics, but this change does not appear to have been matched by a sufficient reappraisal of the value to be gained from domiciliary treatment, as Heaf (1950) has said, "it is possible that the slavish adherence to the prescribing of sanatorium treatment has become a habit, and a more enlightened approach to the management of all cases might be established by asking ourselves if sanatorium treatment is really necessary." These remarks become much more urgent to-day when so many antibiotics are available. There seems little point in insisting that patients should be admitted to hospital merely to fill up beds which are falling empty in increasing numbers.

This is not to deny the use of the sanatorium bed, however. Patients will require admission to hospital where home conditions are unsuitable or where a patient is so seriously ill as to require skilled nursing. In addition, admission to hospital would be essential for surgery. It would seem, indeed, that with the extension of home treatment the use of sanatoria would have to be revised.

It would be much more beneficial to the community at large if the money saved on those hospital beds could be used to provide camera units at every chest clinic so that frequent X-ray examinations were available for contact examination, and also to provide open sessions for general practitioners. Barr and Ritchie (1955) have demonstrated the value of these general practitioner sessions in diagnosis. By using every means at our disposal to find the early patients, it might be possible to diagnose them at such a stage that they could be treated as ambulatory patients or with modified bed rest without admission to a sanatorium.

Summary

With suitable home conditions, it is possible to treat minimal and moderately advanced pulmonary tuberculosis without admission to a sanatorium. The far advanced patient, too, can also receive considerable benefit from home treatment.

The elderly and "chronic" patients are not considered suitable for hospital unless with adverse home conditions.

The value of chemotherapy is discussed; in particular the need for daily streptomycin and long continued treatment is emphasised.

The need for early diagnosis is stressed, and thereby it might be possible to treat most patients at home.

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TUBERCULOSIS AND SYPHILIS

A RECORD OF FOUR CASES

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Every case admitted to hospital, diagnosed as tuberculosis, demands consideration as to whether the diagnosis is correct, and whether any other condition is present.

Frequently the patient derives more benefit from the treatment of an intercurrent condition such as deafness, ocular defects or dental decay, than from the treatment of a tuberculous lesion.

The following cases are recorded becauses of the lesson learnt that although the Wassermann reaction need no longer be done as a routine, it still remains a necessary procedure when any unusual clinical signs are discovered.

Case 1. A man aged 58 suddenly collapsed at home two months before admission. Influenza and later right-sided pneumonia were diagnosed. He became more breathless and his cough and sputum, which he had had for many years, increased. He had occasional aching in the right side of his chest. He was treated with penicillin and his temperature settled, but his general condition deteriorated and he started to hiccough. He was admitted to hospital. At that time he was afebrile, there was free fluid in his abdomen, his liver was moderately enlarged. A leucocyte count showed 20,000 white cells, of which 78 per cent. were polymorphs. His sputum contained no acid-fast bacilli or malignant cells, a fungus was grown on culture. X-ray showed consolidation of the right upper lobe. He was given a further course of penicillin for ten days and then streptomycin for twenty-one days. Three days after admission he developed slight jaundice which persisted for four days. Two weeks after admission he had staining of sputum for ten days.

He improved slowly and was able to sit in a chair. As the possibility of carcinoma of the bronchus was considered, he was transferred here for bronchoscopy about two months after his illness first began. His right upper lobe was still consolidated, his liver was enlarged. There was still some free fluid in his abdomen.

Investigations: Hb. 53 per cent; R.B.C.s 2,500,000; W.B.C.s normal. Cold agglutinations were present. Blood Urea: 24 mg. per cent.; sputum no A.F.B.s or malignant cells. Liver functions test: total serum protein 8·6 g., albumen 1·3 g., globulin 7·3 g., alpha 2·1, beta 1·8, gamma 3·4.

Peritoneal fluid was aspirated and contained a few lymphocytes but no organisms. Following a suggestion by one of my colleagues, a W.R. was performed and was positive on three occasions. Since he had already been given two courses of penicillin and was improving, no further treatment was given. After a further month, X-ray showed the lung lesion to be resolving, the plasma proteins were normal, the free fluid had cleared up. He was discharged a month later. Six months later his X-ray was completely normal.

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PLATE XXIII

FIG. 1.—Case 1 on admission.

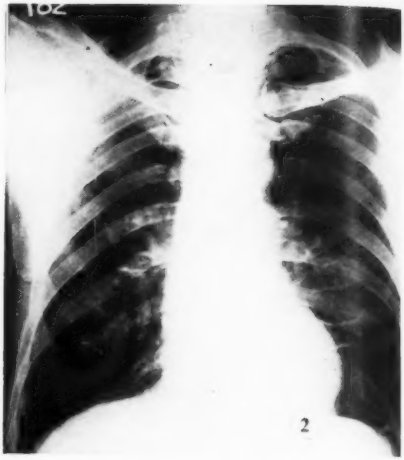

FIG. 2.—Case 1 after eight months.

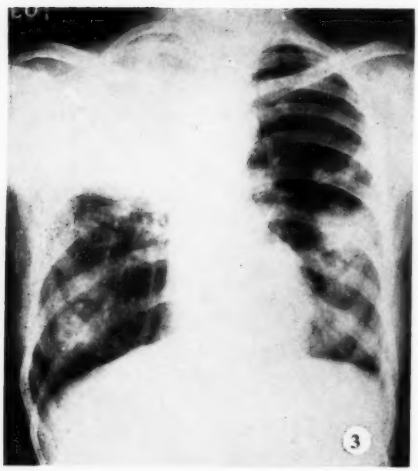

FIG. 3.—Case 2 on admission.

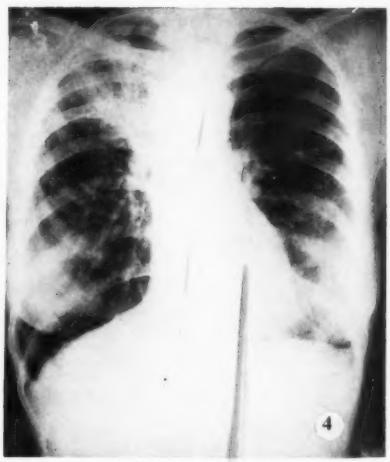

FIG. 4.—Case 2 after eight months' treatment with anti-tuberculous and anti-syphilitic drugs.

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Case 2. A woman aged 39 in domestic service, separated from her husband, cut her leg badly, needing five stitches; she felt no pain. She was given notice and had a nervous breakdown. She was admitted to a mental hospital.

As she had night sweats, she was referred to the Chest Clinic for an X-ray which showed a pneumonic consolidation of the right apex and nodular lesions at the left base.

On admission to hospital she was depressed and unco-operative. She had a hearing aid. Her temperature was 100°, E.S.R. 105 mm. Sputum was positive on two occasions. She was anæmic, Hb. 62 per cent., R.B.C.s 3,230,000. Her pupils were large and irregular, they reacted poorly to light and briskly to accommodation. Her knee and ankle jerks were absent. She did not feel any pain when pricked with a pin in the legs. The W.R. was positive in her blood and C.S.F., the latter also contained slight excess of globulin, and the Lange curve was luetic in type.

Her tuberculosis was treated with I.N.A.H., PAS and streptomycin. Her syphilis with two courses of penicillin. She improved mentally, her pupillary changes cleared up, but the anæsthesia in her legs persisted. The anæmia disappeared, her lung lesions were very slow in improving, but on discharge after eight months they had cleared considerably.

Case 3. A female aged 34 who was examined by Mass X-ray two years previously and tuberculosis was discovered. She had spent five months in a Sanatorium. While she was there she was found to be very deaf and was transferred to the care of an Ear Specialist at a nearby General Hospital for investigation, but no cause was found. After a year back at work her X-rays showed a serious spread and she was admitted to Bevendean Hospital. On admission she was very deaf, her pupils were small and reacted poorly to light but briskly to accommodation. She had diminished sensation to pinprick in her legs. Her sputum was negative, E.S.R. 2 mm., X-ray showed bilateral apical and mid-zone infiltration. Her W.R. was positive on several occasions. She was treated with two courses of penicillin and also I.N.A.H. and streptomycin. Her deafness and other signs in her central nervous system did not alter, so a hearing aid was prescribed. Her chest improved considerably and she was discharged after seven months.

Case 4. A male aged 55 had had tabes dorsalis for at least thirty years, when he was treated with a full course of anti-syphilitic treatment. His W.R. had never been positive. Eight years ago he had a hæmoptysis and advanced pulmonary tuberculosis was discovered. He had a serious relapse and was admitted to hospital. His chest took a very long time to improve. His rombergism was so marked that when he was screened before a pneumoperitoneum refill, special precautions had to be taken to prevent him from falling.

Discussion

When two diseases coincide, it is of importance to have some idea how they react on each other. The result must vary with the degree of activity at the time both of the tuberculosis and of the syphilis. Thus in case 4 the tabes was " burnt out " and probably had no influence on the tuberculosis. The husband of case 3 had a negative W.R., she was therefore suffering probably from a congenital infection, which had little effect on the tuberculosis.

In case 2, however, both diseases were considered to be active and both responded partially to their several treatments. Case 1 was probably a case of syphilitic lung. It is my personal view that the manifestations of tertiary

syphilis are often localised to a particular organ by intercurrent strain, injury or disease; in this case a lower respiratory infection, though here there was in addition a general manifestation—a hepatitis.

A similar case possibly following an infarct was described by Morgan *et al.* (1952) and was removed for fear it might be a neoplasm. Ward Smith *et al.* (1950) described a rounded shadow resembling a tuberculoma or peripheral carcinoma which was removed by lobectomy and proved on section to be a gumma.

The pathology of syphilis of the lung is described by Bruce Pearson and de Navasquez (1938), whose cases were so advanced that they proved fatal.

Fishberg (1932) thought that when established cases of syphilis developed tuberculosis the prognosis was not too bad, the fibrosis that frequently developed in such cases made it difficult to isolate the tubercle bacillus in the sputum, but when a case of pulmonary tuberculosis developed a fresh syphilitic infection, the balance of the resistance of the host to his tuberculosis was upset and the prognosis made worse. Treatment with arsenicals could be harmful but on the whole bismuth was safe. He did not find that tuberculosis caused false positive Wassermann reactions.

Warring (1939) found an incidence of 4 per cent. positive Wassermann reactions in 2,160 sanatorium patients in the U.S.A. He thought that the pulmonary tuberculosis did not respond so favourably.

Our incidence must be very roughly of the order of 1 in 500 patients. From our experience and a survey of the literature it would seem that there is often a considerable time lag before the possibility of syphilis is entertained. It is impossible to say from our small series whether the response to treatment was in any way delayed.

Summary

Four cases of syphilis occurring in the practice of a Chest Hospital are described; three had coincidental tuberculosis, one was probably a case of pulmonary syphilis.

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PULMONARY TUBERCULOSIS UNDER LONG-TERM TREATMENT WITH CORTICOTROPHIN AND CHEMOTHERAPY

A REPORT ON THREE CASES

By Hugh Climie, Geoffrey Beven and S. R. Sims

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Corticotrophin has been blamed for causing reactivation or development of progressive pulmonary tuberculosis during treatment of patients with rheumatoid arthritis (Fred *et al.*, 1951) and the use of this hormone has been frowned upon in some quarters in the presence of tuberculosis (Amer. Trudeau Society, 1952). Others, notably Houghton (1954), have shown that this substance can safely be administered to patients suffering from pulmonary tuberculosis provided antibacterial treatment for the latter is given concurrently. Indeed it appears that corticotrophin enhances the effect of chemotherapy and often alters dramatically the condition of the patient. That it can be given for long periods with apparent benefit in advanced pulmonary tuberculosis, and used in the treatment of rheumatoid arthritis complicated by pulmonary tuberculosis, is shown by the following case summaries.

Case Reports

Case 1. W.B., an engineer aged 45, developed symptoms of rheumatoid arthritis early in 1952. His chest was then radiologically clear, but in February 1953 a radiograph revealed acute exudative tuberculosis in the right upper lobe. His sputum contained tubercle bacilli. On admission to hospital his condition was poor, and gross articular changes of rheumatoid type were present. The E.S.R. was 135 mm. in 1 hour (Westergren). Streptomycin sulphate 1 g. three times weekly, and sodium para-amino salicylate, 18 g. daily, were given. In July he developed typical psoriasis of groins and penis. Phenylbutazone 400 mg. daily was given on 8.8.53 and increased to 600 mg. on 9.9.53, but his arthritis improved little and his psoriasis increased, with severe involvement of the nails. A cavity appeared in the right lung and his condition was visibly deteriorating.

On 14.10.53 the dose of streptomycin was increased to 1 g. daily and on 21.10.53 aqueous corticotrophin 100 units daily (I.M.I. six-hourly) was substituted for phenylbutazone. There was dramatic clinical improvement. Next day his joints had a greater range of movement and were less painful, so that he could sit up by himself. He gained weight rapidly and became very cheerful. The psoriasis began to heal and in about three weeks his E.S.R. decreased from 129 to 11 mm. As some œdema appeared, the dose of corticotrophin was slowly decreased until 20 units daily was reached on 7.11.53, and

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the calcium salt was substituted for sodium PAS. There was radiological improvement in the lungs within a month and this was continued when the corticotrophin was reduced to 15 units daily. The rheumatoid arthritis improved steadily and the psoriasis cleared. On 19.1.54 a pneumoperitoneum was induced, and in mid-February the corticotrophin was gradually decreased and stopped on 1.3.54 when the course had lasted 18 weeks. When all chemotherapy was discontinued on 8.3.54 the tuberculosis was apparently quiescent and the cavity had become a solid focus. He was discharged home in April 1954, but then had a mild relapse of his rheumatoid arthritis and a more severe one of psoriasis, again including the nails. The psoriasis cleared entirely with local treatment and his arthritis slowly improved with aspirin so that he was able to dispense with crutches. In March 1955 he returned to work as a clerk and has remained well.

Case 2. R.C., a chronic alcoholic aged 49, was admitted on 4.12.53, suffering from malnutrition, toxæmia, and probably also "alcohol withdrawal." Extensive chronic bilateral pulmonary tuberculosis with cavitation was found. His temperature was 100° F. and he was about a stone under weight. Streptomycin 1 g. and sodium PAS 15 g. were given daily for 43 days without improvement in his condition; so on 17.1.54 isoniazid 300 mg. daily was added. All three drugs were discontinued on 5.2.54 because of an erythematous rash, although at this time he was still febrile and the X-rays suggested deterioration. The rash subsided but the pyrexia of 102°-103° F. persisted and treatment was, therefore, resumed on 25.2.54 with daily streptomycin, PAS and isoniazid, and the addition of corticotrophin gel 60 units daily, given eight-hourly. The temperature fell to normal in 24 hours, the E.S.R. fell within a week from 58 to 15 mm. and he gained weight steadily. The dose of corticotrophin was reduced to 48 units daily on the fourth day, but when it was further reduced to 30 units on the seventeenth day (15.3.54) the temperature suddenly rose to 102° F., so it was discontinued. After 3 weeks the rash reappeared and PAS was, therefore, omitted. The rash then subsided, but he remained febrile. At this time his tubercle bacilli were sensitive to all three anti-tuberculous drugs.

Corticotrophin was recommenced on 4.5.54 with 60 units daily. The temperature again fell dramatically. The dose of corticotrophin was reduced to 40 units, but the E.S.R. remained high for four months. The dose was therefore increased to 50 units in September, and the E.S.R. gradually fell to 10 mm. over the next 4 months. Calcium benzoyl PAS, 14 gr. daily, was added at this time without a recurrence of rash or pyrexia at the higher dosage of corticotrophin. When the latter was reduced to 45 units daily, however, the temperature soon rose to 102° F. Although there was no rash, the fever subsided when the PAS was stopped. The dose of corticotrophin was steadily diminished and discontinued on 25.4.55, after more than 50 weeks of treatment. The streptomycin which had been given throughout (total amount 354 gm.) was stopped on 13.5.55.

Clinically he has remained very well and his weight has increased by 1½ stones. After the initial deterioration on chemotherapy alone his tuberculosis slowly improved radiologically during the course of corticotrophin and this improvement was maintained. Nevertheless, the disease was still extensive and his sputum contained tubercle bacilli which, however, have failed to grow on prolonged culture.

In August 1955 a pneumoperitoneum was induced and he was getting up for several hours a day.

CASE 3. F.M., a man of 35, was admitted on 9.2.55 with advanced chronic bilateral pulmonary tuberculosis. His temperature was 100° F. and he was about 2 stones under weight. His E.S.R. was 35 mm. and his blood pressure 140/80. The sputum contained tubercle bacilli. Treatment was commenced with daily streptomycin 1 g. and isoniazid 300 mg., but the fever persisted and during the next 7 weeks grave deterioration, both clinical and radiological, occurred.

Therefore from 29.3.55 corticotrophin was given in addition (60 units daily). The temperature fell to normal within 24 hours and almost immediately there was marked clinical improvement; he became jovial and euphoric, and within 14 days his E.S.R. fell from 45 to 7 mm. On 4.4.55 calcium benzoyl PAS (14 g. daily) was commenced. In mid-April he developed œdema and his blood pressure rose to 180/130, so the dose of corticotrophin was gradually reduced to 30 units. However, although his blood pressure soon returned to normal, the patient was not so well. The E.S.R. increased to 22 mm. and the temperature to 99°-101° F. The dose was, therefore, gradually increased until by 16.5.55 he was having 40 units; his temperature then became normal and he remained well. The radiographs suggested steady improvement, and after gradually reducing the corticotrophin over 4 weeks, it was discontinued on 26.9.55 (a course of 26 weeks with streptomycin 232 g.). He was then clinically very well and his chest X-ray showed marked improvement, although there was still some active disease. His sputum was apparently negative and he had gained 3 stones in weight.

Discussion

When severe rheumatoid arthritis is complicated by pulmonary tuberculosis a therapeutic problem arises. Corticotrophin may be of value during severe phases of rheumatoid arthritis and psoriasis (Ormsby and Montgomery, 1954). In case 1 there was dramatic reversal of the progress of all three diseases. It is, therefore, evident that corticotrophin can usefully be given in such circumstances.

The rapid disappearance of tuberculous toxæmia during treatment with corticotrophin has been noted by Houghton (1954), who has also shown that there may be clinical and radiological improvement in cases which were previously deteriorating on streptomycin and PAS alone. Our patients were deteriorating while having various combinations of streptomycin, PAS and isoniazid. Dick (1955) has pointed out that recent lesions may disappear within 2 to 8 weeks of treatment with isoniazid, but in case 3 after using isoniazid with streptomycin for 6 weeks, deterioration continued. In the two cases with advanced disease the deterioration was alarming. They immediately began to improve when corticotrophin was added, and we also found that the course of the disease was profoundly changed. In the cases with fibrotic disease and much destruction, radiological changes were only gradual and limited in extent, which is what would be expected.

Most cases previously reported have had treatment with corticotrophin for much shorter periods than used by us. We gave a longer course (6 months) in case 1, because of rheumatoid arthritis. In case 2 the course was prolonged for 12 months as the patient had extensive disease, a persistently raised E.S.R. and, when the dose was temporarily reduced, he was not so well. In case 3

the course was maintained for 6 months because this patient also had extensive disease and became worse when we tried to reduce the dose; he had occasional slight fever until the fourth month of treatment. Whether these patients really needed such prolonged courses is uncertain, but we formed the opinion that they were all being helped by their treatment and no important complications were seen. At any rate these cases do indicate that prolonged treatment with corticotrophin can be given for pulmonary tuberculosis without harm.

It has been shown that hypersensitivity to anti-tuberculous and other drugs can be suppressed by corticotrophin and that desensitisation may occur during this treatment (Houghton, 1954). Case 2 demonstrates that a minimum dose of corticotrophin is required to suppress completely the signs of hypersensitivity to PAS. When the dose was too low fever and rash developed. Of Houghton's eight cases showing drug hypersensitivity, two failed to become desensitised after two months' treatment with corticotrophin. It is therefore interesting that, even after a course lasting one year, our patient still exhibited hypersensitivity to PAS.

Summary

Three cases of pulmonary tuberculosis having long-term treatment with corticotrophin and chemotherapy are described.

Clinical and radiological improvement occurred when corticotrophin was added to the treatment of patients previously deteriorating on streptomycin and PAS or isoniazid. Long-term treatment up to one year is possible.

Treatment with corticotrophin can be used with safety for rheumatoid arthritis and psoriasis, complicated by pulmonary tuberculosis, provided that adequate chemotherapy is given.

We gratefully acknowledge the advice of Dr. Q. Hobson, Dr. D. Doran and Dr. F. Jenner, and we thank Sister Gibbons, Sister McNamara and the nursing staff for their help and care of the patients.

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CORTISONE AND CHEMOTHERAPY IN PULMONARY TUBERCULOSIS

By J. B. Cochran, J. A. Hislop and Christopher Clayson

From Dumfries and Galloway Sanatorium, Lochmaben

This paper is a report of the treatment of nineteen patients with pulmonary tuberculosis by cortisone combined with standard chemotherapy. Our preliminary findings have already been reported (Cochran, 1954). The initial results were sufficiently encouraging to warrant an extended trial.

There is clinical and experimental evidence that cortisone has a deleterious influence in tuberculosis (Popp *et al.*, 1951; Doerner *et al.*, 1951; King *et al.*, 1951; Fred *et al.*, 1951; Hart and Rees, 1950; Michael *et al.*, 1950). A coincident tuberculous lesion even if it is inactive, is considered to be a contra-indication to the clinical use of cortisone. An investigation of the effects of cortisone combined with standard chemotherapy in pulmonary tuberculosis can be considered from two aspects. Firstly, can cortisone be safely administered to the tuberculous subject provided it is covered by anti-tuberculous drugs? Secondly, will cortisone, by its lysing and inhibiting effect on granulation tissue, bring the tubercle bacilli into more direct contact with the anti-tuberculous drugs and thus enhance chemotherapeutic action?

In American literature there are a few reports of small trials of both cortisone and ACTH either alone or in combination with streptomycin and para-amino salicylic acid (PAS) in the treatment of advanced pulmonary tuberculosis (Le Maistre *et al.*, 1951; Tompsett *et al.*, 1950; U.S. Vet. Admin. Quart. Progress Report 1950). There was temporary and often marked symptomatic improvement, but little evidence that the course of the disease had been altered. In this country Houghton (1954) has investigated combined corticotrophin therapy and chemotherapy in pulmonary tuberculosis with special reference to hypersensitive reactions. In addition to the suppression of drug hypersensitivity by the hormone Houghton observed marked symptomatic improvement in severely ill patients, and there was also evidence of radiographic improvement in patients who had not previously responded well to streptomycin and PAS alone.

Methods

The potential danger of cortisone in pulmonary tuberculosis necessitated at first the use of small doses or the selection of advanced cases with poor prognosis. Later, as confidence with the hormone grew, less severe disease was treated with higher doses and certain pathological types of disease which might be expected to respond to combined treatment were selected. In all but one patient the criterion for cortisone treatment was a radiological assessment that the disease had become static. Cortisone was given orally for two

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months in doses of 12·5 to 100 mg. daily. Thirteen patients received 50 to 100 mg. daily. Eleven patients were receiving their initial course of chemotherapy and the drugs were continued unchanged throughout the trial. Seven patients had had previous courses of chemotherapy, but where possible the drugs being used prior to cortisone were continued throughout. One patient had cortisone from the beginning of treatment. In all patients chemotherapy was continued unchanged for at least two months after stopping cortisone. The routine observations made were twice daily rectal temperatures and pulse rates, a weekly clinical examination including weight and B.S.R. (Westergren), fortnightly chest X-rays and sputum examination by direct smear and culture. Clinical details of the nineteen patients are shown in Table 1.

TABLE 1.—CLINICAL DETAILS OF PATIENTS TREATED WITH CORTISONE

Patient	*Sex*	*Age*	*Type of Disease*	*Dosage of Cortisone mg./day*	*CHEMOTHERAPY*		
					Previous	*With cortisone*	*Bacterial resistance*
1	M	44	Bilat. hæmatogenous	12·5	3/12 S3H20P	⟶S3H20P	
2	M	44	Chronic fibrotic bilat. excavation	25	3/12 S20P 5/12 20PH	S3H	Present to 0·3 μg./ml. S
3	M	62	Chronic fibrotic tension cav.	25	—	S320P	
4	F	27	Chronic fib.-caseous bilat. excavation	50	3½/12 S3H18P	⟶S3H18P	
5	M	33	Chronic fib.-caseous bilat. excavation	50	3/12 S312P 6/12 H 4/12 S3H	S320P	Present to 17 μg./ml. S
6	M	33	Chronic fib.-caseous bilat. excavation	50-100	3/12 H. 3/12 S20P 2/12 S3H12P 4/12 12PH	S3H	Present to 50 μg./ml. H 17 μg./ml. S
7	F	46	Acute caseous unilobar	50-100	3½/12 S3H18P	⟶S3H18P	
8	F	28	Chronic fibrotic bilat. tension cav.	50-100	3/12 S25P. 3/12 H 3/12 18PH 2/12 S218P	⟶S218P	
9	M	53	Chronic indolent mid-zone lesions	50-100	3/12 S3H	⟶S3H	
10	F	35	Acute bronchogenic bilat. extensive	50-75	4/12 S3H20P	⟶S3H20P	Present to 0·3 μg./ml.
11	F	25	Acute bronchogenic bilat. extensive	50-75	7/12 S320P	⟶S320P	
12	F	24	Bilat. hæmatogenous	50	3/12 S320P	⟶S320P	
13	F	16	Acute bronchogenic bilat. excavation	50-75	9/12 S320P	⟶S320P	
14	M	21	Tuberculoma	25-50	3½/12 S320P	⟶S320P	
15	M	20	Bilat. upper zone indolent infiltrates	100	1/12 18PH 4½/12 S20P	⟶S20P	
16	F	15	Primary T.B.	50	3½/12 S320P	⟶S320P	
17	M	13	Primary T.B.	50	4/12 S3H12P 1/12 20PH	⟶20PH	
18	M	12	Primary T.B.	25-50	2/12 S3(½ g.)12P 2/12 S3(½ g.)H	⟶S3(½ g.)H(100)	
19	M	3	Primary T.B.	25	2½/12 S3(½ g.)H(50)	⟶S3(½ g.)H(50)	

S=Streptomycin 1 g. daily.
S2=Streptomycin 1 g. twice weekly.
S3=Streptomycin 1 g. on alternate days.
H=INAH 200 mg. daily.
12, 18 or 20P=PAS 12, 18 or 20 g. daily.
⟶=Indicates continuity of chemotherapy

General Symptomatic Effects: Weight and B.S.R.

The patients receiving 50 to 100 mg. of cortisone daily experienced a feeling of well-being with increase of appetite and strength. This general effect was most pronounced in toxic patients. During combined treatment there was an early and progressive increase in weight. In fifteen patients the gain in weight during two months' cortisone exceeded the weight gain during the preceding two months. At two months after stopping cortisone the gain in weight is largely maintained in thirteen patients (Table 2).

There was a prompt and often dramatic fall in the B.S.R. with cortisone. On stopping the drug the B.S.R. in general returned to its previous level; this applied especially to the more advanced cases (Table 2).

Effect of Cortisone on the Bacteriology of the Sputum

Ten patients were sputum (or gastric lavage) negative direct and on culture prior to cortisone and remained so during the full four months of the trial (Table 2). Seven patients were sputum (or gastric lavage) positive direct prior to and at the end of the cortisone course; of these patients, three were negative direct and on culture at two months after stopping cortisone. Complete results are not available for one patient who died and another who took her own discharge. Patient 19 (aged 3 years) had no sputum and gastric lavage was not attempted.

Thus cortisone has had little or no effect on the bacteriology of the sputum and the results at fortnightly intervals confirm this. Probably the most significant finding is that the sputum (or gastric lavage) examined at fortnightly intervals has remained negative direct and on culture in ten patients of whom eight had 50 to 100 mg. of cortisone daily for two months.

Radiological Effects of Cortisone

The cases can be conveniently considered in five disease groups. Acute disease was judged to have been present for less than two years and chronic disease for more than two years. Improvement after two months of combined treatment is assessed as significant if such improvement occurred more rapidly or to a greater degree than could have been expected on chemotherapy alone. On this basis eleven of nineteen patients have benefited from cortisone. Each group will be considered separately.

Primary Tuberculosis

Two of four patients showed significant improvement with cortisone (patients 18 and 19). In both there was evidence of persistent atelectasis despite chemotherapy, and in one (18) there was additional parenchymal infiltration. It is not known whether cortisone relieved bronchial stenosis due to glandular pressure or endobronchial disease. Although no improvement occurred in patient 17, who had a persistent collapse of the right middle lobe, the bronchoscopic findings (Dr. B. R. Hillis) are of interest. Prior to cortisone bronchoscopy revealed frank granulations on the wall of the right main

TABLE 2.—EFFECT OF CORTISONE ON B.S.R. WEIGHT CHANGE AND BACTERIOLOGY OF SPUTUM

Patient	Cortisone daily mg.	B.S.R.			Weight change			Sputum					
								Before cortisone		After 2 months' cortisone		2 Months after cortisone	
		Before cortisone (mm./hr.)	After 2 months' cortisone (mm./hr.)	2 Months after cortisone (mm./hr.)	In 2 months before cortisone (lb.)	In 2 months of cortisone (lb.)	In 2 months after cortisone (lb.)	dir.	cult.	dir.	cult.	dir.	cult.
1	12·5	37	24	20	+6	+12	−4	—	—	—	—	—	—
2	25	29	13	23	−1	+10	+4	+		+		+	
3	25	28	9	8	−5	+5	+4	+		+		—	—
4	50	18	12	7	+9	+13	+1	G.L.+		G.L.+		G.L.—	—
5	50	19	11	15	0	0	0	+		+		+	
6	50-100	70	—	—				+					
7	50-100	21	11	19	+6	+10	−1	—	—	—	—	—	—
8	50-100	34	14	42	−3	+5	−2	+		+		+	
9	50-100	10	10	14	0	+7	−2	—	—	—	—	—	—
10	50-75	51	9	17	+2	+13	+2	G.L.+		G.L.+		G.L.—	—
11	50-75	15	9	I.D.	+2	+7	I.D.	+		+			
12	50	14	5	7	+9	+4	0	G.L.—	—	G.L.—	—	G.L.—	—
13	50-75	19	9	9	+6	+8	−2	G.L.—	—	G.L.—	—	G.L.—	—
14	25-50	1	1	1	0	+5	−5	—	—	—	—	—	—
15	100	2	0	2	0	+8	−7	—	—	—	—	—	—
16	50	9	6	6	+1	+8	0	G.L.—	—	G.L.—	—	G.L.—	—
17	50	31	11	6	+1	+7	+4	G.L.—	—	G.L.—	—	G.L.—	—
18	25-50	15	15	10	+4	+6	−2	G.L.—	—	G.L.—	—	G.L.—	—
19	25	—	—	—	0	0	0						

I.D.=irregular discharge. + Positive. — Negative. G.L.=gastric lavage.

bronchus which prevented visualisation of the middle lobe orifice. After cortisone a repeat bronchoscopy showed that the granulations had disappeared and the middle lobe orifice was clearly seen and completely stenosed.

Chronic Tuberculosis

Three of six patients showed significant improvement This was most striking in patient 3, who had fibrotic disease of the right upper lobe with a large tension cavity known to have been present for at least three years. Cortisone 25 mg. daily was given with the initial course of chemotherapy and within two months the cavity had disappeared. This was confirmed by tomography. Patient 8 had bilateral tension cavities which had remained unchanged over many months despite chemotherapy. In the right lung the cavity measured 1 cm. in diameter, while in the left lung the diameter was 3 inches. After cortisone the smaller cavity closed and the patient was later able to undergo surgical treatment for the large cavity in the left lung. Of those patients who failed to respond to cortisone, all had advanced bilateral disease with excavation and persistently positive sputum with partially drug-resistant bacilli.

Patient 6 died after six weeks' combined treatment. His lungs were grossly diseased with multiple areas of softening and he was considered to be in the terminal phase of his illness. Although resistant to the standard drugs, as a last resort we decided to use cortisone 100 mg. daily combined with streptomycin and INAH. The initial symptomatic improvement was remarkable. The temperature, which had been between 100° and 103° F. for many months, fell to normal in two days. The appetite greatly improved, dyspnœa lessened and his strength increased. This improvement was not maintained. Increasing dyspnœa was attributed to fluid retention and cortisone dosage was reduced to 50 mg. daily. Pyrexia reappeared and there was a sudden onset of severe diarrhœa with blood and mucus which could not be controlled and continued till death. Post-mortem examination (Dr. A. L. Scott) showed advanced bilateral phthisis with extensive caseation and cavitation. There were no tuberculous lesions elsewhere. On histological examination of the lungs the striking feature was the degree of vascularity associated with the caseous lesions. The walls around the cavities showed little fibrosis and both epithelioid cells and lymphocytes were scanty. It is impossible to say what part cortisone played in these appearances, as they may well have resulted from INAH (Dick, 1953) or very low resistance. Before starting cortisone the patient was considered to be in the terminal phase of his illness and it is difficult to say whether or not the drug hastened his death.

Acute Tuberculosis

Three of four patients underwent significant improvement with cortisone. In two of these three patients (10, 11) the infection was bilateral and extensive and appeared static after four and seven months' chemotherapy respectively. At the start of combined treatment the lesions, although static, appeared exudative in character and the subsequent improvement entailed a loss of radiological "fluffiness." Patient 7 had a tuberculous pneumonic lesion of

the right upper lobe with partial atelectasis and central softening. After one month's chemotherapy definite resolution had occurred, but X-rays at two and three months showed little change and the disease was judged to be static. A two months' course of cortisone (75 mg. daily) resulted in obvious further resolution amounting to about 50 per cent. when compared with the previous area of static disease. Patient 13 had very destructive bilateral disease which had undergone considerable improvement after nine months' chemotherapy. No further improvement occurred with cortisone and a residual cavity in the right upper lobe was unaffected.

Indolent Infiltrates

A residual tuberculomatous lesion (patient 14) was unaltered by cortisone. Patient 15 had residual bilateral upper zone infiltrates which appeared quiescent and static after four months' chemotherapy. Cortisone caused complete resolution of opacities in the first right interspace, but the other lesions were unchanged. Patient 9 had a left mid-zone infiltration of low activity which had undergone no appreciable radiological change during two years' Out-Patient follow-up. A course of three months' chemotherapy followed by two months' combined treatment were without effect on the lesions.

Hæmatogenous Tuberculosis

The two patients in this group (1 and 12) had subacute miliary lesions symmetrically distributed throughout the upper two-thirds of both lungs. Both had three months' chemotherapy prior to cortisone treatment. Patient 1 was the first patient treated and received the small dose of 12·5 g. cortisone daily. The radiological clearing which occurred with cortisone was considerable and accelerated when compared with the progress during the first three months. Patient 12 had 50 mg. cortisone daily and there was no doubt as to the accelerated radiological improvement which resulted.

Toxic Effects of Cortisone

Excluding the one fatality of which the relationship to cortisone is uncertain, no serious toxic effects were noted. The higher dosage schedule of 50 to 100 mg. cortisone daily caused some rounding of the facial contours. There was no evidence of exacerbation of either the pulmonary disease or unsuspected lesions elsewhere. Hæmatogenous dissemination did not occur.

Discussion

It is unwise to make dogmatic conclusions from a chemotherapeutic trial which has not been conducted under strictly controlled conditions. At the start of our investigations such a trial of combined cortisone and chemotherapy in tuberculosis seemed impractical and perhaps dangerous. It was decided to proceed on the lines described and to regard the investigation as preliminary.

Probably the most significant finding which emerges from this trial is that

cortisone in doses up to 100 mg. daily for two months can be safely administered to the tuberculous patient so long as the hormone is covered by suitable combinations of the standard drugs, streptomycin, PAS and INAH. A tuberculous lesion, active or quiescent, is universally considered to be a definite contra-indication to cortisone treatment. Our observations indicate that cortisone with chemotherapeutic cover can be safely used where there is a coincident tuberculous lesion.

Definite symptomatic improvement results from cortisone treatment. This is most obvious in toxic patients. Subsequent deterioration does not occur on cortisone withdrawal. The great majority of patients gain weight which is largely maintained; for this purpose alone a course of the hormone may be justified in patients with advanced disease who are failing to gain weight.

In the assessment of radiological improvement it must be emphasised that many patients were considered to be static after relatively short courses of chemotherapy lasting three to six months. There is no doubt that in most of these patients further improvement would have occurred on continued chemotherapy. Our criterion of significant improvement with cortisone is the assessment of accelerated improvement greater than would have been expected on chemotherapy alone. It appears that in post-primary tuberculosis combined treatment has achieved its best results in acute disease. In this group three of four patients underwent significant improvement. The disease in these patients was judged to have been present for less than two years. On this basis the two cases of hæmatogenous tuberculosis can be included to give significant improvement in five of six patients with acute disease. On close scrutiny of X-ray films, it is seen that in general cortisone has had its maximal effect on the softer or more fluffy opacities. In a few patients resolution has occurred within the first month or even the first fortnight of combined treatment. There was no radiological evidence of lysis of well-formed fibrous tissue.

In chronic tuberculosis the radiological effects were disappointing. Of six patients treated, five had advanced bilateral disease with excavation, and of these four were " poor chronics " despite prolonged sanatorium treatment and chemotherapy. In three patients there was bacillary resistance to one or more of the standard drugs. Only three patients showed significant improvement and all had effective chemotherapeutic cover. It is of course in this group that symptomatic improvement is greatest, and in view of the gross destructive pulmonary lesions it is perhaps not surprising that cortisone has given disappointing radiological results.

Our experience with localised indolent infiltrates has also been disappointing. We had hoped that cortisone might prove of value in the resolution of the residual tuberculomatous lesion which is a potential focus of reactivation. Only one of three patients with this type of lesion showed improvement and this was confined to one lung only.

In primary tuberculosis significant improvement was assessed in two of four patients in whom there was evidence that cortisone had relieved persistent bronchial obstruction. The bronchoscopic findings in one patient suggested that cortisone had caused resolution of tuberculous granulation tissue.

Conclusions

Cortisone in doses up to 100 mg. daily for two months covered by anti-tuberculous chemotherapy can be safely administered to patients with pulmonary tuberculosis whether the disease is acute or chronic, active or quiescent. This combined treatment causes symptomatic improvement with increase in appetite and gain in weight. On withdrawal of cortisone no obvious clinical deterioration occurs and the gain in weight is largely maintained. For its general effect alone cortisone may have a place in the treatment of advanced and chronic disease. Significant although not dramatic radiological improvement can be expected to occur in over 50 per cent. of patients, and the hormone appears especially to hasten the resolution of acute lesions. There is evidence that cortisone may be of value in relieving the bronchial stenosis of primary disease. The indolent infiltrate or tuberculomatous lesion is unaffected, but further study of this group is required.

Summary

This paper is a report of the treatment of pulmonary tuberculosis by cortisone combined with standard chemotherapy. The clinical, bacteriological and radiological findings are presented in nineteen patients. Cortisone can be safely administered to the tuberculous subject if it is covered by anti-tuberculous chemotherapy. Symptomatic improvement is commonly observed and weight gain is largely permanent. Eleven of nineteen patients were considered to have shown accelerated improvement with cortisone and the best results occurred in relatively acute lesions.

Supplies of cortisone were generously made available by the Medical Research Council.

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ACUTE PANCREATITIS FOLLOWING ADMINISTRATION OF ISONICOTINIC ACID HYDRAZIDE

REPORT OF A CASE

By Ian Dickson

From The Cheshire Joint Sanatorium

Since the advent of therapy with isonicotinic acid hydrazide (INAH) for tuberculosis, there have been a number of cases in which a marked influence on carbohydrate metabolism has been noted. Luntz and Smith (1953) observed the presence of reducing substances in the urine of 5 out of 24 patients receiving the drug. In addition, they showed that INAH caused raised blood sugar levels in both the diabetic and non-diabetic patient. Most clinicians will have experienced the increased difficulty in stabilising and maintaining in a stable state the tuberculous diabetic who is receiving INAH.

There appears to be some evidence that the drug has a direct inhibiting action on the islets of Langerhans, but the following history suggests the possibility in some cases of a direct effect on all the pancreatic tissue.

The patient—a married woman, aged 48—commenced with symptoms of tiredness, lassitude and malaise in January 1953. Her only previous medical history was of diphtheria at the age of 5. In August 1953 she noticed cough, loss of weight and thirst. She was referred to the Chest Clinic in November 1953 and was admitted to hospital for investigation, where pulmonary tuberculosis and diabetes were diagnosed.

The diabetes was stabilised on 35 units of insulin-zinc suspension and a 12-line Lawrence diet, although there had been the usual difficulty in maintaining the stability when PAS and INAH were commenced just prior to transfer to sanatorium.

In January 1954 she was transferred to sanatorium, when the E.S.R. was 60 mm. 2 hours (Westergren), the sputum was positive for tubercle bacilli on direct examination and X-ray showed heavy infiltration of the right upper zone with cavitation, and some infiltration and cavitation of the left upper zone. On January 11, 1954, daily PAS 15 gm., streptomycin 1 g., and INAH 250 mg. were begun. There was an immediate need for increased insulin and on January 23, 1954, there was a sharp febrile attack with rigors, nausea and vomiting, and loose motions.

On January 24, 1953, an erythematous rash developed, and all chemotherapy and antibiotics were stopped. Antihistamine drugs were given, and by January 31, 1954, the temperature was normal and the rash had subsided. By this time, however, the patient was receiving more than double the amount of insulin she had been receiving on admission (76 units) and continued to require this amount despite the stopping of the INAH. In all other respects,

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however, the patient began to improve, and on March 4, 1954, the right phrenic nerve was crushed and a pneumoperitoneum induced.

On reviewing progress in May, it was considered advisable to try to desensitise the patient to streptomycin (at that time considered to have been the cause of her drug reaction in January). It was intended to give the patient two to three days of INAH alone before initiating desensitising doses of streptomycin, and accordingly on May 24 she was given 150 mg. of INAH. That evening there was pyrexia and the patient complained of nausea and malaise. The evening specimen of urine contained a trace of sugar. The same dosage of INAH was repeated on May 25, 26 and 27, again with the symptoms of nausea, malaise and with pyrexia.

On May 27 the midday specimen showed both sugar and acetone, and extra soluble insulin was given. Despite this, there was a heavy deposit of sugar in afternoon and evening specimens.

On May 28 the diabetes became completely uncontrolled, with severe glycosuria and acetonuria. The blood sugar rose from its pre-INAH level of 116 mg. per cent. (fasting) to 430 mg. per cent., and despite intensive measures with saline-lactate and Hartman's transfusions and the exhibition of large doses of soluble insulin it remained high.

The patient was transferred as an urgency to the diabetic unit of a General Hospital and, despite similar intensive measures, died on June 2, 1954.

Post-mortem showed the expected lesions in both lungs. There was an acute œsophagitis and the peritoneum contained about a quart of turbid fluid. The omentum showed fat necrosis and the pancreas was virtually destroyed by an acute pancreatitis.

Apart, therefore, from the usual difficulty in stabilising diabetics who are receiving INAH, any symptoms suggesting a more extensive involvement of the pancreas, such as nausea and vomiting, diarrhœa or severe abdominal pain, should be regarded with utmost suspicion, and taken as a strong indication for stopping the INAH therapy.

Summary

A case of a tuberculous diabetic receiving isoniazid therapy is described in whom great difficulty was experienced in stabilising the diabetes.

Recommencement of isoniazid therapy after an interval of four months resulted in an acute pancreatitis and death of the patient.

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REVIEWS OF BOOKS

Subphrenic Abscess. By H. R. S. HARLEY, M.S., F.R.C.S. Oxford: Blackwell Scientific Publications. 1955. Pp. 216+11: 41 illustrations and 51 tables. 35s. net.

Subphrenic abscess formation is far from common, so that any one surgeon is unlikely to see many patients with the condition. An authoritative consideration of all the problems presented by this is therefore most welcome, and in this, his main endeavour, Mr. Harley has succeeded fully and he has produced a most valuable monograph.

There is a clear account of the anatomy of the subphrenic spaces, followed by an interesting discussion of the routes of spread to these spaces, with emphasis upon the direct, intraperitoneal pathway. An alarmingly high percentage of subphrenic abscesses are accompanied by some complication, and perhaps the most valuable section of this book is the clear and detailed consideration of the various intrathoracic complications. The section dealing with the clinical aspects is less satisfactory, the main facts being submerged in such a wealth of analytical detail that a true picture only emerges intermittently, and to a lesser extent the same applies to the section on radiology. With regard to treatment, Mr. Harley advocates strongly that all these abscesses should be drained via an extraserous approach. The arguments in favour of this approach are set out convincingly, the operations involved described clearly and succinctly, and the section on the results of treatment provides powerful support for this method of treatment.

Mr. Harley's monograph is based on his study of 188 case histories of patients with subphrenic abscesses, most of whom " were admitted to, and treated in, Voluntary Teaching Hospitals in or near London." However, in view of the striking effect of antibiotics in this condition, it is a pity that the period in which these cases were treated is not specified. Further, it is clear that in the majority of instances the data and conclusions are based on the retrospective study of other peoples' case notes. The weaknesses of this form of investigation are well known, yet despite the extreme detail of the analytical breakdown of his data, Mr. Harley makes but one passing reference to this matter.

These criticisms aside, the book can be recommended as an excellent, exhaustive account of the subject. It is admirably printed in clear type, with full references but surprisingly no index. Whilst perhaps a little full for students and even those reading for postgraduate examinations, this monograph should prove of great value to all surgeons concerned with the management of this type of case, and will surely become the standard work of reference on the subject.

L. P. LE QUESNE.

Diseases of the Chest. By H. CORWIN HINSHAW, M.D., Ph.D., Clinical Professor of Medicine, Stamford University, and L. Henry Garland, M.B., B.Ch., Clinical Professor of Radiology, Stamford University. Philadelphia and London: W. B. Saunders Company. 1956. Pp. 727, 634 illustrations. 105s. net.

The authors state that their reason for producing still another textbook on diseases of the chest is to keep pace with the unparalleled and impressive

advances which have occurred in the field of thoracic disorders during the past ten years. They lay stress on diagnosis as the cornerstone of modern medicine, and radiology rather than the elicitation of physical signs occupies the position of prominence in the examination of the patient; in fact in many cases the physical signs receive but scant attention.

The combination of a physician and a radiologist as authors of this text-book emphasises the important part X-ray examinations now play in thoracic medicine and surgery.

Dr. Hinshaw wins our kindly feelings by revealing himself as a humane man who is concerned with the patient's feelings as well as with the nature and extent of his disease. The psychological aspects in pulmonary tuberculosis are not overlooked, for we read: " The chaplain has saved many a life by restoring peace of mind and rational thinking." Further, when discussing how the patient should be told that he has pulmonary tuberculosis, the author writes: " The physician is loath to impart the information and rarely can accomplish the task with equanimity, regardless of how many times he has faced the problem before." An interesting chapter is included dealing with the pulmonary and associated changes in the collagen diseases. These include periarteritis nodosa, disseminated lupus erythematosus, scleroderma, rheumatic fever and rheumatoid arthritis. There are also descriptions of rarer diseases such as necrotising granulomatosis, coccidiomycosis, nocardiosis and histoplasmosis. In considering sarcoidosis the authors are of the opinion that the cause is absolutely unknown, and they devote some space to refuting the view, which is still put forward, that sarcoidosis is an aberrant form of tuberculosis. The Kveim cutaneous test for sarcoidosis is also summarily dismissed as " too cumbersome to be of practical value in medical practice."

There are the printer's errors to which we are accustomed in these days, which appear to result from the type being dropped after the corrected page proofs have been sent in. Thus at the bottom of page 158 we meet with such strange words as " bronrteal," " nega-e," " baihi," and " dilvetation."

The book is well produced, the X-ray reproductions are on the whole very good, and the references add to the value of the text. The authors are to be congratulated on having produced an excellent book which can be confidently recommended.

G. E. BEAUMONT.

Pulmonary Circulation and Respiratory Function. A Symposium held at Queen's College, Dundee. Edinburgh: Livingstone. Pp. 44. 12s. 6d.

This monograph is remarkable for the breadth of its approach to the problems of pulmonary circulation and respiratory function. It embodies the views of physicians, surgeons, clinical research workers, physiologists and pathologists. Each has approached the subject from a different angle and the very divergence of these helps to underline the magnitude and complexity of the subject and brings to the fore the important problems to which a solution must be sought.

The central problem discussed is the role of the autonomic nervous system in controlling pulmonary vascular tone. Whether pulmonary vascular tone plays any part in the regulation of the pulmonary circulation in health remains undecided, although most contributors were agreed that it does so in disease. Pulmonary hypertension was primarily of two varieties, functional and anatomical. The importance of anatomical vascular changes in the lung in cor-

pulmonale seen in miners was contrasted with the functional nature of pulmonary hypertension in emphysema heart disease.

The practical and theoretical importance of pulmonary function tests is discussed. It is suggested that in the normal subject there is uneven ventilation of the lung, which might require autonomic control of selective blood supply to different portions of the lung.

There are some interesting sections on the importance of tonus of the right ventricular outflow tract in regulating the function of the right ventricle, on the chemical mechanism of control of closure of the ductus arteriosus in the new-born lamb, and on mechanical breathing apparatus. The nitrous oxide method of measuring pulmonary capillary flow is described, which has been shown to have a pulsatile nature. Dr. Averill Liebow, the Praelector in Pathology at the University of St. Andrews in 1955, discusses the collateral circulation resulting from ligature of all the pulmonary veins in the dog and suggests various possible therapeutic applications of this procedure.

The book contains, in addition to the contributions of the principal speakers, a full report of the discussion, and a list of the members of the symposium is given at the beginning.

PATRICK MOUNSEY.

Brompton Hospital Reports. Volume XXIII. Aldershot: Gale and Polden Ltd. 1954. Pp. ix+326. Illus. 15s. net.

The Brompton Hospital Reports have this year a wider scope, including within their pages work published by members of the staffs of the London Chest Hospital and the Institute of Diseases of the Chest, as well as of the Brompton alone. Many of the papers have been previously published. A notable exception is Dr. F. H. Young's contribution on " The Use of Tuberculin in Combination with Streptomycin as a Precursor of Operation," which has certainly an original viewpoint. It is pleasing to read in these days the well-balanced views of Dr. Howard Nicholson on the value of artificial pneumothorax in the treatment of pulmonary tuberculosis.

As is to be expected from such an informed group of contributors, there is pleasure in the mere reading of the other articles, whether or not one agrees with the views presented. It is difficult to single out any particular contribution, for all deal with current problems of great clinical significance.

Dr. Paul Wood's article, " An Appreciation of Mitral Stenosis," is outstanding, and a classic of its kind, which the reviewer has enormously enjoyed reading again. The contributions on chronic bronchitis repay a second reading, for they are both instructive and practical. " Benign Tumours of the Lung," by Sir Clement Price Thomas, and the views of J. W. Clegg on " Ulcerocaseous Tuberculous Bronchitis," are most informative.

As usual, the production of the volume is admirable, and the editors are to be congratulated once again on their achievement.

PHILIP ELLMAN.

Tuberculose Utéro-Annexielle. By JULES BRET and ROBERT LEGROS. Paris: Masson et Cie. Paper covers, 248 pages, illustrated. 1,600 fr.

This monograph is an excellent summary of modern practice in the investigation and treatment of tuberculosis of the female genital organs, particularly of the silent forms of the disease which are now more often encountered than advanced cases. It is based on a personal experience of about 100 cases. Professor Bernard Duperrat has contributed a well illustrated description of the

pathology, and in the clinical sections the frequency with which pelvic tuberculosis is associated with other manifestations of the disease is emphasised. Chemotherapy is described.

In a few respects practice in France appears to differ from that in this country. It is surprising that the authors report so little success in recovering the tubercle bacillus by culture or inoculation of endometrial fragments. The risk of lipiodol salpingography in this condition is perhaps understated. Cœlioscopy and vaginal smear diagnosis are mentioned. The authors report several cases of pregnancy following pelvic tuberculosis, but the diagnosis was only completely proved by biopsy in one case.

The book is beautifully printed on excellent paper, but it is surely time that French printers learnt to cut the edges of the pages; an appreciable part of the time spent on reading was wasted on this irritating task. A good bibliography is added.

STANLEY CLAYTON.

Ergebnisse der Gesamten Tuberkuloseforschung. Band XIII. Stuttgart: Georg Thieme Verlag. 1956. Pp. viii+659. Illus. DM. 96.

This book deals with tuberculosis of all parts of the body, and particularly with modern forms of treatment. All kinds of chemotherapy and modern surgical methods are included, as well as recent chemical and microscopical methods in relation to clinical examination.

In this short review we have not space to mention by name the nineteen extremely interesting contributions by various authors. The subjects range from the morphological picture of tuberculosis under chemotherapy, through the effects of chemotherapy on all types of tuberculosis, to the influence such therapy has had on the surgical treatment of tuberculosis.

To illustrate the style of the various chapters, we need only refer to the one on *Chemotherapy and Antibiotic Therapy of Pulmonary Tuberculosis*, by J. Hein and W. Stecher (pp. 479-560 inclusive of references). When we realize that the comprehensiveness of this chapter is repeated in all the others, we can form an idea of the enormous field covered in this volume. We must also mention the excellent microphotographs, the abundance of references and the useful indices provided.

This book is a result of an ambitious endeavour by the authors to satisfy an obvious want, and we think it is a successful one. The fact that it is written in German should not prevent its being understood by a great many English-speaking specialists in various parts of the world, who are concerned with this subject in whole or in part.

F. PARKES WEBER.

BOOKS RECEIVED

The following books have been received and reviews of some of them will appear in subsequent issues.

The Practice of Medicine. Ed. by John S. Richardson. London: J. and A. Churchill Ltd. 1956. Pp. viii+1,076. Illus. 40s.

An Inquiry into Health Visiting. Report of a Working Party on the Field of Work, Training and Recruitment of Health Visitors. London: Her Majesty's Stationery Office. 1956. Pp. xiii+183. 6s. 6d. net.

Chest Surgery for Nurses. By J. Leigh Collis and L. E. Mabbit. London: Baillière, Tindall and Cox. 1956. Pp. viii+196. Illus. 15s.

Tuberculosis in the Commonwealth 1955. N.A.P.T. Great Britain: Waterlow and Sons Ltd. Pp. xii+507. Illus.

Principles of Chest X-ray Diagnosis. By George Simon. London: Butterworth and Co. (Publishers) Ltd. 1956. Pp. x+183. Illus. 50s. net.

Tuberculosis Control in Manitoba 1955. Annual Report of the Sanatorium Board of Manitoba. Winnipeg, Manitoba. 1956. Pp. 56. Illus. 30s.

Airborne Contagion and Air Hygiene. By William Firth Wells. Harvard University Press. 1955. Pp. 29+421. Illus. 48s. net.

Nouvelle Orientation du Traitement du Mal de Pott de l'Adulte. S. de Sèze and J. Debeyre. France: Masson et Cie. 1956. Pp. 102. Illus. 900 fr.

Cœur et Poumons. P. Soulie and E. Brial, J. Carlotti, J. di Matteo, Fr. Joly, P. Laurens, A. Piton, J.-R. Sicot, J. Delarue, G. Brouet, R. Depierre, M. Bariety, J. Paillas. France: Masson et Cie. 1956. Pp. 224. Illus. 1,600 fr.

NOTES AND NOTICES

THE THORACIC SOCIETY

THE Summer Meeting will be held in Aberdeen on July 20 and 21, 1956.

There will be a discussion on " Assisted Respiration," the opening speakers being: Dr. T. Anderson, Dr. B. A. Sellick, Dr. A. B. Kinnier Wilson, Dr. R. A. Beaver, Professor Ian Donald and Dr. Lawson Davidson.

There will be communications on:

(1) " Myocardial Depletion of Potassium and Glucose during Experimental Hypothermia, and the Use of these Substances in the Prevention and Treatment of Ventricular Fibrillation," the speaker being Mr. G. E. Mavor.

(2) " Open Healing of Tuberculous Cavities," the speakers being Dr. R. Y. Keers on " Clinical and Radiological Features " and Dr. Lynne Reid on " Pathology of Resected Specimens." Dr. R. W. Riddell will open the discussion.

(3) " Blood-stained Pleural Effusions with Special Reference to those due to Neoplastic Conditions of the Pleura," the speakers being Dr. Joseph Smart and Dr. K. F. W. Hinson.

There will be short papers on:

(1) "Reflex Cardiac Arrhythmias and Arrest," by Dr. A. W. Raffan.
(2) "Aortic Aneurisms," by Mr. P. L. Brunnen.
(3) "The Anatomy of the Pulmonary Septa," by Dr. Lynne Reid.
(4) "Tumours in the Posterior Diaphragmatic Sulcus and their Radiography," by Dr. Eric Hudson.
(5) "Pneumoconiosis caused by Scouring Products," by Dr. David Caldwell.

THE BRITISH TUBERCULOSIS ASSOCIATION

THE Annual Conference was held in Bristol from June 27 to 30. Among the subjects discussed were the following:

The Application of our Present Epidemiological Knowledge to the Problem of the Eradication of Tuberculosis. By Dr. A. L. Cochrane.

THE PRESENT POSITION OF COLLAPSE THERAPY IN PULMONARY TUBERCULOSIS

Artificial Pneumothorax. By Dr. A. T. M. Roberts.
Artificial Pneumoperitoneum. By Dr. Harold G. Trimble (California, U.S.A.).
Surgical Collapse. By Mr. R. H. R. Belsey.
Results of Resection. By Mr. F. Ronald Edwards.
Congenital Tuberculosis. By Dr. Beryl Corner.
Tuberculosis of the Endometrium. By Dr. A. M. Sutherland.
B.C.G. The Medical Research Council Report. By Dr. P. D'Arcy Hart, Dr. T. M. Pollock, Dr. Ian Sutherland, Dr. Mary Farquharson, Professor Wilfred Gaisford.
Preparation and Control of B.C.G. Vaccine. By Dr. Knud Tolderlund (State Serum Institute, Copenhagen).

REHABILITATION

The Clinical Problem. By Dr. A. F. Foster-Carter. Remploy and the Employment of the Tuberculous. By Brigadier T. F. Kennedy, O.B.E.
Rehabilitation Programme in Canada. By Dr. Lachlan Macpherson (New Brunswick, Canada).

TUBERCULOSIS EDUCATIONAL INSTITUTE

POST-GRADUATE Courses on Tuberculosis in Children and Young Adults are being held in Sheffield in September of this year.

There are two courses, one from September 10 to 14, for Doctors, and another for Nurses and Social Workers from September 11 to 14.

Full details can be obtained from the Tuberculosis Educational Institute, Tavistock House North, Tavistock Square, London, W.C.1.

RETIREMENT

SIR WELDON DALRYMPLE-CHAMPNEYS, Deputy Chief Medical Officer of the Ministry of Health, will be retiring from the public service at the end of July this year.

Sir Weldon was appointed Deputy Chief Medical Officer of the Ministry in 1940. In 1939 he was Principal Regional Medical Officer for the South-eastern Region. He was Honorary Physician to King George VI from 1941 to 1944.